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**MUTATIONS RESPONSIBLE FOR ATTENUATION IN MEASLES VIRUS OR
HUMAN RESPIRATORY SYNCYTIAL VIRUS SUBGROUP B**

Abstract:

Abstract of WO9949017

Isolated, recombinantly-generated, attenuated measles viruses and respiratory syncytial subgroup B viruses having defined attenuating mutations are described. Vaccines are formulated comprising such viruses and a physiologically acceptable carrier. The vaccines are used for immunizing an individual to induce protection against measles virus or respiratory syncytial subgroup B virus.

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<p>3A A2 B1 2B 2B33F 2B33F TS+ 18537</p> <p>← N-P-M-SH ← P-M-SH ← M-SH ← SH</p>			

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MUTATIONS RESPONSIBLE FOR ATTENUATION IN MEASLES VIRUS
OR HUMAN RESPIRATORY SYNCYTIAL VIRUS SUBGROUP B

Field Of The Invention

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This invention relates to isolated, recombinantly-generated, attenuated measles virus or human respiratory syncytial virus subgroup B having specified attenuating mutations. This invention was made with Government support under a grant awarded by the Public Health Service. The Government has certain rights in the invention.

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Background Of The Invention

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Enveloped, negative-sense, single stranded RNA viruses are uniquely organized and expressed. The genomic RNA of negative-sense, single stranded viruses serves two template functions in the context of a nucleocapsid: as a template for the synthesis of messenger RNAs (mRNAs) and as a template for the synthesis of the antigenome (+) strand. Negative-sense, single stranded RNA viruses encode and package their own RNA dependent RNA Polymerase. Messenger RNAs are only synthesized once the nucleocapsid has entered the cytoplasm of the infected cell. Viral replication occurs after synthesis of the mRNAs and requires the continuous synthesis of viral proteins. The newly synthesized antigenome (+) strand serves as the template for generating further copies of the (-) strand genomic RNA.

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The polymerase complex actuates and achieves transcription and replication by engaging the cis-acting signals at the 3' end of the genome, in particular, the promoter region. Viral genes are then

- 2 -

transcribed from the genome template unidirectionally from its 3' to its 5' end. There is always less mRNA made from the downstream genes (e.g., the polymerase gene (L)) relative to their upstream neighbors (i.e., the nucleoprotein gene (N)). Therefore, there is always a gradient of mRNA abundance according to the position of the genes relative to the 3'-end of the genome.

Based on the revised reclassification in 1993 by the International Committee on the Taxonomy of Viruses, an Order, designated Mononegavirales, has been established. This Order contains three families of enveloped viruses with single stranded, nonsegmented RNA genomes of minus polarity (negative-sense). These families are the Paramyxoviridae, Rhabdoviridae and Filoviridae. The family Paramyxoviridae has been further divided into two subfamilies, Paramyxovirinae and Pneumovirinae. The subfamily Paramyxovirinae contains three genera, *Paramyxovirus*, *Rubulavirus* and *Morbillivirus*. The subfamily Pneumovirinae contains the genus *Pneumovirus*.

The new classification is based upon morphological criteria, the organization of the viral genome, biological activities and the sequence relatedness of the genes and gene products. The morphological distinguishing feature among enveloped viruses for the subfamily Paramyxovirinae is the size and shape of the nucleocapsids (diameter 18nm, 1nm in length, pitch of 5.5 nm), which have a left-handed helical symmetry. The biological criteria are: 1) antigenic cross-reactivity between members of a genus, and 2) the presence of neuraminidase activity in the genera *Paramyxovirus*, *Rubulavirus* and its absence in genus *Morbillivirus*. In addition, variations in the coding potential of the P gene are considered, as is the presence of an extra gene (SH) in Rubulaviruses.

- 3 -

Pneumoviruses can be distinguished from Paramyxovirinae morphologically because they contain narrow nucleocapsids. In addition, pneumoviruses have major differences in the number of protein-encoding
5 cistrons (10 in pneumoviruses versus 6 in Paramyxovirinae) and an attachment protein (G) that is very different from that of Paramyxovirinae. Although the paramyxoviruses and pneumoviruses have six proteins that appear to correspond in function (N, P, M, G/H/HN,
10 F and L), only the latter two proteins exhibit significant sequence relatedness between the two subfamilies. Several pneumoviral proteins lack counterparts in most of the paramyxoviruses, namely the nonstructural proteins NS1 and NS2, the small
15 hydrophobic protein SH, and a second protein M2. Some paramyxoviral proteins, namely C and V, lack counterparts in pneumoviruses. However, the basic genomic organization of pneumoviruses and paramyxoviruses is the same. The same is true of
20 rhabdoviruses and filoviruses. Table 1 presents the current taxonomical classification of these viruses, together with examples of each genus.

Table 1

25 Classification of Nonsegmented, negative-sense, single stranded RNA Viruses of the Order Mononegavirales
Family Paramyxoviridae

Subfamily Paramyxovirinae

Genus Paramyxovirus

30 Sendai virus (mouse parainfluenza virus type 1)

Human parainfluenza virus (PIV) types 1 and 3

Bovine parainfluenza virus (BPV) type 3

35 Genus Rubulavirus

- 4 -

Simian virus 5 (SV) (Canine
parainfluenza virus type 2)
Mumps virus
Newcastle disease virus (NDV) (avian
Paramyxovirus 1)
Human parainfluenza virus types 2, 4a
and 4b
Genus *Morbillivirus*
Measles virus (MV)
Dolphin Morbillivirus
Canine distemper virus (CDV)
Peste-des-petits-ruminants virus
Phocine distemper virus
Rinderpest virus
Subfamily Pneumovirinae
Genus *Pneumovirus*
Human respiratory syncytial virus (RSV)
Bovine respiratory syncytial virus
Pneumonia virus of mice
Turkey rhinotracheitis virus
Family Rhabdoviridae
Genus *Lyssavirus*
Rabies virus
Genus *Vesiculovirus*
Vesicular stomatitis virus
Genus *Ephemerovirus*
Bovine ephemeral fever virus
Family Filoviridae
Genus *Filovirus*
Marburg virus

For many of these viruses, no vaccines of any
kind are available. Thus, there is a need to develop
vaccines against such human and animal pathogens. Such
vaccines would have to elicit a protective immune

- 5 -

response in the recipient. The qualitative and quantitative features of such a favorable response are extrapolated from those seen in survivors of natural virus infection, who, in general, are protected from reinfection by the same or highly related viruses for some significant duration thereafter.

A variety of approaches can be considered in seeking to develop such vaccines, including the use of: (1) purified individual viral protein vaccines (subunit vaccines); (2) inactivated whole virus preparations; and (3) live, attenuated viruses.

Subunit vaccines have the desirable feature of being pure, definable and relatively easily produced in abundance by various means, including recombinant DNA expression methods. To date, with the notable exception of hepatitis B surface antigen, viral subunit vaccines have generally only elicited short-lived and/or inadequate immunity, particularly in naive recipients.

Formalin inactivated whole virus preparations of polio (IPV) and hepatitis A have proven safe and efficacious. In contrast, immunization with similarly inactivated whole viruses such as respiratory syncytial virus and measles virus vaccines elicited unfavorable immune responses and/or response profiles which predisposed vaccinees to exaggerated or aberrant disease when subsequently confronted with the natural or "wild-type" virus.

Early attempts (1966) to vaccinate young children used a parenterally administered formalin-inactivated RSV vaccine. Unfortunately, several field trials of this vaccine revealed serious adverse reactions -- the development of a severe illness with unusual features following subsequent natural infection with RSV (Bibliography entries 1,2). It has been

- 6 -

suggested that this formalinized RSV antigen elicited an abnormal or unbalanced immune response profile, predisposing the vaccinee to RSV disease (3,4).

Thereafter, live, attenuated RSV vaccine candidates were generated by cold passage or chemical mutagenesis. These RSV strains were found to have reduced virulence in seropositive adults.

Unfortunately, they proved either over or under-attenuated when given to seronegative infants; in some cases, they also were found to lack genetic stability (5,6). Another vaccination approach using parenteral administration of live virus was ineffective and efforts along this line were discontinued (7).

Notably, these live RSV vaccines were never associated with disease enhancement as observed with the formalin-inactivated RSV vaccine described above. Currently, there are no RSV vaccines approved for administration to humans, although clinical trials are now in progress with cold-passaged, chemically mutagenized strains of RSV designated A2 and B-1.

Appropriately attenuated live derivatives of wild-type viruses offer a distinct advantage as vaccine candidates. As live, replicating agents, they initiate infection in recipients during which viral gene products are expressed, processed and presented in the context of the vaccinee's specific MHC class I and II molecules, eliciting humoral and cell-mediated immune responses, as well as the coordinate cytokine and chemokine patterns, which parallel the protective immune profile of survivors of natural infection.

This favorable immune response pattern is contrasted with the delimited responses elicited by inactivated or subunit vaccines, which typically are largely restricted to the humoral immune surveillance arm. Further, the immune response profile elicited by

- 7 -

5 some formalin inactivated whole virus vaccines, e.g.,
measles and respiratory syncytial virus vaccines
developed in the 1960's, have not only failed to
provide sustained protection, but in fact have led to a
predisposition to aberrant, exaggerated, and even fatal
illness, when the vaccine recipient later confronted
the wild-type virus.

10 While live, attenuated viruses have highly
desirable characteristics as vaccine candidates, they
have proven to be difficult to develop. The crux of
the difficulty lies in the need to isolate a derivative
of the wild-type virus which has lost its disease-
producing potential (i.e., virulence), while retaining
sufficient replication competence to infect the
15 recipient and elicit the desired immune response
profile in adequate abundance.

Historically, this delicate balance between
virulence and attenuation has been achieved by serial
passage of a wild-type viral isolate through different
20 host tissues or cells under varying growth conditions
(such as temperature). This process presumably favors
the growth of viral variants (mutants), some of which
have the favorable characteristic of attenuation.
Occasionally, further attenuation is achieved through
25 chemical mutagenesis as well.

This propagation/passage scheme typically
leads to the emergence of virus derivatives which are
temperature sensitive, cold-adapted and/or altered in
their host range -- one or all of which are changes
30 from the wild-type, disease-causing viruses -- i.e.,
changes that may be associated with attenuation.

Several live virus vaccines, including those
for the prevention of measles and mumps (which are
paramyxoviruses), and for protection against polio and
35 rubella (which are positive strand RNA viruses), have

- 8 -

been generated by this approach and provide the
mainstay of current childhood immunization regimens
throughout the world.

5 Nevertheless, this means for generating
attenuated live virus vaccine candidates is lengthy
and, at best, unpredictable, relying largely on the
selective outgrowth of those randomly occurring genomic
mutants with desirable attenuation characteristics.
10 The resulting viruses may have the desired phenotype *in*
vitro, and even appear to be attenuated in animal
models. However, all too often they remain either
under- or overattenuated in the human or animal host
for whom they are intended as vaccine candidates.

15 Even as to current vaccines in use, there is
still a need for more efficacious vaccines. For
example, the current measles vaccines provide
reasonably good protection. However, recent measles
epidemics suggest deficiencies in the efficacy of
current vaccines. Despite maternal immunization, high
20 rates of acute measles infection have occurred in
children under age one, reflecting the vaccines'
inability to induce anti-measles antibody levels
comparable to those developed following wild-type
measles infection (8,9,10). As a result, vaccine-
25 immunized mothers are less able to provide their
infants with sufficient transplacentally-derived
passive antibodies to protect the newborns beyond the
first few months of life.

30 Acute measles infections in previously
immunized adolescents and young adults point to an
additional problem. These secondary vaccine failures
indicate limitations in the current vaccines' ability
to induce and maintain antiviral protection that is
both abundant and long-lived (11,12,13). Recently, yet
35 another potential problem was revealed. The

- 9 -

hemagglutinin protein of wild-type measles isolated over the past 15 years has shown a progressively increasing distance from the vaccine strains (14). This "antigenic drift" raises legitimate concerns that the vaccine strains may not contain the ideal antigenic repertoire needed to provide optimal protection. Thus, there is a need for improved vaccines.

Rational vaccine design would be assisted by a better understanding of these viruses, in particular, by the identification of the virally encoded determinants of virulence as well as those genomic changes which are responsible for attenuation.

Previously, in U.S. provisional application 60/026,823 and International application PCT/US97/16718, both of which are hereby incorporated by reference, the generation and isolation of recombinantly-generated, attenuated, nonsegmented, negative-sense, single stranded RNA viruses of the Order Mononegavirales having at least one attenuating mutation in the 3' genomic promoter region and having at least one attenuating mutation in the RNA polymerase gene was disclosed. Identification of attenuating changes in other regions of the genomes of these viruses would further assist rational vaccine design.

Summary Of The Invention

Accordingly, it is an object of this invention to identify additional regions of the genomes of measles virus and human respiratory syncytial virus subgroup B where mutations result in attenuation of those viruses.

It is a further object of this invention to produce recombinantly-generated viruses which

- 10 -

incorporate such attenuating mutations in their genomes.

It is still a further object of this invention to formulate vaccines containing such attenuated viruses.

These and other objects of the invention as discussed below are achieved by the generation and isolation of recombinantly-generated, attenuated, measles virus or human respiratory syncytial virus subgroup B having specified attenuating mutations.

In the case of measles virus, one or more attenuating mutations are selected from the group consisting of: (1) for the N gene, nucleotide changes which produce changes in an amino acid selected from the group consisting of residues 129 (glutamine → lysine), 148 (glutamic acid → glycine) and 479 (serine → threonine); (2) for the P gene, nucleotide changes which produce changes in an amino acid selected from the group consisting of residues 225 (glutamic acid → glycine), 275 (cysteine → tyrosine) and 439 (leucine → proline); (3) for the C gene, nucleotide changes which produce changes in an amino acid selected from the group consisting of residues 73 (alanine → valine), 104 (methionine → threonine) and 134 (serine → tyrosine); and (4) for the F gene-end signal (the cis-acting transcription termination signal), the change at nucleotide 7243 (T → C), where these nucleotides, as well as others delineated in this application (unless stated otherwise), are presented in positive strand, antigenomic, that is, message (coding) sense.

In the case of human respiratory syncytial virus subgroup B, there is an attenuating mutation in the M gene-end signal (the cis-acting transcription

- 11 -

termination signal) at nucleotide 4199 (T → C), where these nucleotides are presented in positive strand, antigenomic, that is, message (coding) sense.

5 In another embodiment of this invention, these attenuated measles or human respiratory syncytial subgroup B viruses are used to prepare vaccines which elicit a protective immune response against the wild-type form of each virus.

10 In yet another embodiment of this invention, an isolated, positive strand, antigenomic message sense nucleic acid molecule (or an isolated, negative strand genomic sense nucleic acid molecule) having the complete viral nucleotide sequence (whether of wild-type virus or virus attenuated by non-recombinant
15 means) is manipulated by introducing one or more of the attenuating mutations described in this application to generate an isolated, recombinantly-generated attenuated measles or human respiratory syncytial subgroup B virus. Each attenuated virus is then used
20 to prepare vaccines which elicit a protective immune response against the wild-type form of each virus.

Brief Description Of The Figures

25 Figure 1 depicts the passage history of the Edmonston measles virus (15). The abbreviations have the following meanings: HK - human kidney; HA - human amnion; CE(am) - chick embryo; CEF - chick embryo fibroblast; DK - dog kidney; WI-38 - human diploid
30 cells; SK - sheep kidney; * - plaque cloning. The number following each abbreviation represents the number of passages.

35 Figure 2 depicts a map of the measles virus genome showing putative cis-acting regulatory elements at and near the genome and antigenome termini. Top - a

- 12 -

schematic map of the measles virus genome, beginning at the 3' end with 52 nucleotides of leader sequence (l) and ending at the 5' terminus with 37 nucleotides of trailer sequence (t). Gene boundaries are denoted by vertical bars; below each gene is the number of
5 cistronic nucleotides. Bottom - an expanded schematic view of the 3' extended genomic promoter regions of genome and antigenome, showing the position and sequence of the two highly conserved domains, A and B.
10 The intervening intergenic trinucleotide is denoted as well. Nascent 5' RNAs encompassing the A' to B' regions are presumed to contain the regulatory sequence at which the N protein encapsidation initiates.

Figure 3 depicts a genetic map of the RSV subgroup B wild-type strains designated 2B and 18537 (top portion), the intergenic sequences of those strains (middle portion) and the 68 nucleotide overlap between the M2 and L genes (bottom portion). The RSV 2B strain has six fewer nucleotides in the G gene,
15 encoding two fewer amino acid residues in the G protein, as compared to the 18537 strain. The 2B strain has 145 nucleotides in the 5' trailer region, as compared to 149 nucleotides in the 18537 strain. The 2B strain has one more nucleotide in each of the NS-1,
20 NS-2 and N genes, and one fewer nucleotide in each of the M and F genes, as compared to the 18537 strain.
25

Figure 4 depicts a Northern blot analysis of poly (A)+ RNA isolated from Vero cells infected with RSV subgroup A and B viruses. A 1.5 hour
30 autoradiograph of the blot is shown. Lanes 1-2 contain RNA isolated from cells infected with RSV subgroup A strains (lane 1, 3A; lane 2, A2). Lanes 3-7 contain RNA isolated from cells infected with RSV subgroup B strains: lane 3, B1; lane 4, 2B; lane 5, 2B33F; lane
35 6, 2B33F TS(+); lane 7, 18537. Monocistronic M gene

- 13 -

and bicistronic M:SH gene transcripts are indicated by arrows.

Figure 5 depicts a ribonuclease protection assay of poly (A)+ RNA extracted from Vero cells infected with RSV subgroup B wild-type 2B, mutant 2B33F, and 2B33F TS(+) revertant viruses to assess the ratio of monocistronic M and SH mRNAs to bicistronic M:SH transcripts for each virus. A 3 hour autoradiograph of the gel is shown. Protected probe fragments are indicated by arrows. Radiolabelled RNA markers (M) were included as size standards: Lane 1, yeast RNA minus RNase; lane 2, yeast RNA plus RNase; lane 3, 2B RNA plus RNase; lane 4, 2B33F RNA plus RNase; lane 5, 2B33F TS+ RNA plus RNase; lane 6, yeast RNA plus RNase; lane 7, yeast RNA minus RNase. RSV 2B-specific probe was used in lanes 1-3 and 2B33F-specific probe was used in lanes 4-7.

Figure 6 depicts a Northern blot analysis of poly (A)+ RNA isolated from Vero cells infected with RSV subgroup A and B viruses. A 1.5 hour autoradiograph of the blot is shown. Lanes 1-2 contain RNA isolated from cells infected with RSV subgroup A strains (lane 1, 3A; lane 2, A2). Lanes 3-7 contain RNA isolated from cells infected with RSV subgroup B strains (lane 3, B1; lane 4, 2B; lane 5, 2B33F; lane 6, 2B33F TS(+); lane 7, 18537). Monocistronic SH gene and bicistronic M:SH gene transcripts are indicated by arrows.

Detailed Description Of The Invention

Transcription and replication of negative-sense, single stranded RNA viral genomes are achieved through the enzymatic activity of a multimeric protein

- 14 -

acting on the ribonucleoprotein core (nucleocapsid). Naked genomic RNA cannot serve as a template. Instead, these genomic sequences are recognized only when they are entirely encapsidated by the N protein into the nucleocapsid structure. It is only in that context that the genomic and antigenomic terminal promoter sequences are recognized to initiate the transcription or replication pathways.

All paramyxoviruses require the two viral proteins, L and P, for these polymerase pathways to proceed. The pneumoviruses, including RSV, also require the transcription elongation factor, M2, for the transcriptional pathway to proceed efficiently. Additional cofactors may also play a role, including perhaps the virus-encoded NS1 and NS2 proteins, as well as perhaps host-cell encoded proteins.

However, considerable evidence indicates that it is the L protein which performs most, if not all, the enzymatic processes associated with transcription and replication, including initiation, and termination of ribonucleotide polymerization, capping and polyadenylation of mRNA transcripts, methylation and perhaps specific phosphorylation of P proteins. The L protein's central role in genomic transcription and replication is supported by its large size, sensitivity to mutations, and its catalytic level of abundance in the transcriptionally active viral complex (16).

These considerations led to the proposal that L proteins consist of a linear array of domains whose concatenated structure integrates discrete functions (17). Indeed, three such delimited, discrete elements within the negative-sense virus L protein have been identified based on their relatedness to defined functional domains of other well-characterized proteins. These include: (1) a putative RNA template

- 15 -

recognition and/or phosphodiester bond formation domain; (2) an RNA binding element; and (3) an ATP binding domain. All prior studies of L proteins of nonsegmented negative-sense, single stranded RNA viruses have revealed these putative functional elements (17).

Without being bound by the following, it is reasonable to presume that these non-protein coding, promoter and other cis-acting genomic regulatory domains are important determinants of the efficiency with which transcription and replication by measles virus (MV) and other viruses of the Order Mononegavirales are actualized, in association with the L protein, and that they may therefore be virulence determinants for these viruses as well.

In summary, the invention is believed to encompass a set of changes in several measles virus genes and one cis-acting regulatory domain, and one change in an RSV subgroup B cis-acting regulatory domain, which result in attenuation of each virus while retaining sufficient ability of the virus to replicate. Therefore, as part of a rational vaccine design, such mutations are introduced to provide the desired balance of replication efficiency and immunogenicity: so that the virus vaccine is no longer able to produce disease, yet retains its capacity to infect the vaccinee's cells, to express sufficiently abundant gene products to elicit the full spectrum and profile of desirable immune responses, and to reproduce and disseminate sufficiently to maximize the abundance of the immune response elicited.

Animal studies have demonstrated a decrease in viral replication sufficient to avoid illness but adequate to elicit the desired immune response. This likely represents a decrease in transcription, a

- 16 -

decrease in gene expression of virally encoded proteins, and/or a decrease in antisense templates and, therefore, the production of fewer new genomes. The resulting attenuated viruses are significantly less virulent than the wild-type.

The attenuating mutations described herein may be introduced into viral strains by two methods:

(1) Conventional means such as chemical mutagenesis during virus growth in cell cultures to which a chemical mutagen has been added, selection of virus that has been subjected to passage at suboptimal temperature in order to select temperature sensitive and/or cold adapted mutations, identification of mutant virus that produce small plaques in cell culture, and passage through heterologous hosts to select for host range mutations. These viruses are then screened for attenuation of their biological activity in an animal model. Attenuated viruses are subjected to nucleotide sequencing of their coding and integenic regions to locate the sites of attenuating mutations. Once this has been done, method (2) is then carried out.

(2) A preferred means of introducing attenuating mutations comprises making predetermined mutations using site-directed mutagenesis. These mutations are identified either by method (1) or by reference to closely-related viruses whose attenuating mutations are already known. One or more mutations as defined herein are introduced into measles virus or RSV subgroup B strains. Cumulative effects of different combinations of coding and non-coding changes can also be assessed.

The mutations to the N, P and/or C genes and/or the F gene-end signal of measles virus, or to the M gene-end signal of RSV subgroup B are introduced by standard recombinant DNA methods into a DNA copy of

- 17 -

the viral genome. This may be a wild-type or a modified viral genome background (such as viruses modified by method (1)), thereby generating a new virus. Infectious clones or particles containing these attenuating mutations are generated using the cDNA "rescue" system, which has been applied to a variety of viruses, including Sendai virus (18); measles virus (19); respiratory syncytial virus (20); PIV-3 (21); rabies (22); vesicular stomatitis virus (VSV) (15); and rinderpest virus (23); these references are hereby incorporated by reference. See, for measles virus rescue, published International patent application WO 97/06270, designating the United States (24); for RSV rescue, published International patent application WO 97/12032, designating the United States (25); these applications are hereby incorporated by reference.

Briefly, all Mononegavirales rescue systems can be summarized as follows: Each requires a cloned DNA equivalent of the entire viral genome placed between a suitable DNA-dependent RNA polymerase promoter (e.g., the T7 RNA polymerase promoter) and a self-cleaving ribozyme sequence (e.g., the hepatitis delta ribozyme) which is inserted into a propagatable bacterial plasmid. This transcription vector provides the readily manipulable DNA template from which the RNA polymerase (e.g., T7 RNA polymerase) can faithfully transcribe a single-stranded RNA copy of the viral antigenome (or genome) with the precise, or nearly precise, 5' and 3' termini. The orientation of the viral genomic DNA copy and the flanking promoter and ribozyme sequences determine whether antigenome or genome RNA equivalents are transcribed. Also required for rescue of new virus progeny are the virus-specific trans-acting proteins needed to encapsidate the naked, single-stranded viral antigenome or genome RNA

- 18 -

transcripts into functional nucleocapsid templates:
the viral nucleocapsid (N or NP) protein, the
polymerase-associated phosphoprotein (P) and the
polymerase (L) protein. These proteins comprise the
5 active viral RNA-dependent RNA polymerase which must
engage this nucleocapsid template to achieve
transcription and replication.

The trans-acting proteins required for
measles virus rescue are the encapsidating protein N,
10 and the polymerase complex proteins, P and L. For RSV,
the virus-specific trans-acting proteins include N, P
and L, plus an additional protein, M2, the RSV-encoded
transcription elongation factor.

Typically, these viral trans-acting proteins
15 are generated from one or more plasmid expression
vectors encoding the required proteins, although some
or all of the required trans-acting proteins may be
produced within mammalian cells engineered to contain
and express these virus-specific genes and gene
20 products as stable transformants.

The typical (although not necessarily
exclusive) circumstances for rescue include an
appropriate mammalian cell milieu in which T7
polymerase is present to drive transcription of the
25 antigenomic (or genomic) single-stranded RNA from the
viral genomic cDNA-containing transcription vector.
Either cotranscriptionally or shortly thereafter, this
viral antigenome (or genome) RNA transcript is
encapsidated into functional templates by the
30 nucleocapsid protein and engaged by the required
polymerase components produced concurrently from co-
transfected expression plasmids encoding the required
virus-specific trans-acting proteins. These events and
processes lead to the prerequisite transcription of
35 viral mRNAs, the replication and amplification of new

- 19 -

genomes and, thereby, the production of novel viral progeny, i.e., rescue.

For the rescue of rabies, VSV and Sendai, T7 polymerase is provided by recombinant vaccinia virus VTF7-3. This system, however, requires that the rescued virus be separated from the vaccinia virus by physical or biochemical means or by repeated passaging in cells or tissues that are not a good host for poxvirus. For MV cDNA rescue, this requirement is avoided by creating a cell line that expresses T7 polymerase, as well as viral N and P proteins. Rescue is achieved by transfecting the genome expression vector and the L gene expression vector into the helper cell line. Advantages of the host-range mutant of the vaccinia virus, MVA-T7, which expresses the T7 RNA polymerase, but produces little or no infectious progeny in mammalian cells, are exploited to rescue RSV, Rinderpest virus and MV. After simultaneous expression of the necessary encapsidating proteins, synthetic full length antigenomic viral RNA are encapsidated, replicated and transcribed by viral polymerase proteins and replicated genomes are packaged into infectious virions. In addition to such antigenomes, genome analogs have now been successfully rescued for Sendai and PIV-3 (21,26).

The rescue system thus provides a composition which comprises a transcription vector comprising an isolated nucleic acid molecule encoding a genome or antigenome of a nonsegmented, negative-sense, single stranded RNA virus of the Order Mononegavirales having (a) for measles virus, at least one attenuating mutation in the N, P or C genes or the F gene-end signal; and (b) for RSV subgroup B, at least one attenuating mutation in the M gene-end signal, together with at least one expression vector which comprises at

- 20 -

least one isolated nucleic acid molecule encoding the trans-acting proteins necessary for encapsidation, transcription and replication (e.g., N, P and L for measles virus; N, P, L and M2 for RSV). Host cells are then transformed or transfected with the at least two expression vectors just described. The host cells are cultured under conditions which permit the co-expression of these vectors so as to produce the infectious attenuated virus.

The rescued infectious virus is then tested for its desired phenotype (temperature sensitivity, cold adaptation, plaque morphology, and transcription and replication attenuation), first by *in vitro* means. The mutations in the N, P or C genes or the F gene-end signal of measles virus and in the M gene-end signal of RSV subgroup B are also tested using the minireplicon system where the required trans-acting encapsidation and polymerase activities are provided by wild-type or vaccine helper viruses, or by plasmids expressing the N, P and different L genes harboring gene-specific attenuating mutations (19,27,83).

If the attenuated phenotype of the rescued virus is present, challenge experiments are conducted with an appropriate animal model. Non-human primates provide the preferred animal model for the pathogenesis of human disease. These primates are first immunized with the attenuated, recombinantly-generated virus, then challenged with the wild-type form of the virus. Monkeys are infected by various routes, including but not limited to intranasal, intratracheal or subcutaneous routes of inoculation (28). Experimentally infected rhesus and cynomolgus macaques have also served as animal models for studies of vaccine-induced protection against measles (29). For evaluating attenuation levels of RSV mutants, the

- 21 -

cotton rat or mouse models may also be used (30,31). Protection is measured by such criteria as disease signs and symptoms, survival, virus shedding and antibody titers. If the desired criteria are met, the
5 attenuated, recombinantly-generated virus is considered a viable vaccine candidate for testing in humans. The "rescued" virus is considered to be "recombinantly-generated", as are the progeny and later generations of the virus, which also incorporate the attenuating
10 mutations.

Even if a "rescued" virus is underattenuated or overattenuated relative to optimum levels for vaccine use, this is information which is valuable for developing such optimum strains.

15 Optimally, a codon containing an attenuating point mutation may be stabilized by introducing a second or a second plus a third mutation in the codon without changing the amino acid encoded by the codon bearing only the attenuating point mutation.

20 Infectious virus clones containing the attenuating and stabilizing mutations are also generated using the cDNA "rescue" system described above.

In one embodiment of the invention, measles virus mutations are assessed, because sequence data are
25 now available as described herein for the disease-causing wild-type virus and for the disease-preventing vaccines which have a demonstrated history of efficacy.

Measles virus was first isolated in tissue culture in 1954 (32) from an infected patient named
30 David Edmonston. This Edmonston strain of measles became the progenitor for many live-attenuated measles vaccines including Moraten, which is the current vaccine in the United States (Attenuvax™; Merck Sharp & Dohme, West Point, PA) and was licensed in 1968 and has
35 proven to be efficacious.

- 22 -

Aggressive immunization programs instituted in the mid to late 1960s resulted in the precipitous drop in reported measles cases from near 700,000 in 1965 to 1500 in 1983. In parallel, other vaccine strains were also developed from the Edmonston strain (see Fig. 1), Schwarz (Institut Merieux, Lyon, France), Zagreb (Zagreb, Yugoslavia) and AIK-C (Japan). These other vaccines have also proven to be efficacious and have been used extensively. An early, reactogenic, underattenuated vaccine strain (Rubeovax™: Merck Sharp & Dohme; this may be the same as the Edmonston B strain) produced measles-like illness in children and its use thus was discontinued. It, however, was further attenuated successfully to produce the Moraten vaccine strain (see Fig. 1) (33). Live measles virus vaccine provides a success story of the development of an efficacious vaccine and provides a model for understanding the molecular mechanisms of viral vaccine attenuation among nonsegmented, negative-sense, single stranded RNA viruses.

Because of its significance as a major cause of human morbidity and mortality, measles virus (MV) has been quite extensively studied. MV is a large, relatively spherical, enveloped particle composed of two compartments, a lipoprotein membrane and a ribonucleoprotein particle core, each having distinct biological functions (34). The virion envelope is a host cell-derived plasma membrane modified by three virus-specified proteins: The hemagglutinin (H; approximately 80 kilodaltons (kD)) and fusion (F_{1,2}; approximately 60 kD) glycoproteins project on the virion surface and confer host cell attachment and entry capacities to the viral particle (16). Antibodies to H and/or F are considered protective since they neutralize the virus' ability to initiate

- 23 -

infection (35,36,37). The matrix (M; approximately 37 kD) protein is the amphipathic protein lining the membrane's inner surface, which is thought to orchestrate virion morphogenesis and thus consummate virus reproduction (38). The virion core contains the 15,894 nucleotide long genomic RNA upon which template activity is conferred by its intimate association with approximately 2600 molecules of the approximately 60 kD nucleocapsid (N) protein (39,40,41). Loosely associated with this approximately one micron long helical ribonucleoprotein particle are enzymatic levels of the viral RNA dependent RNA polymerase (L; approximately 240 kD) which in concert with the polymerase cofactor (P; approximately 70 kD), and perhaps yet other virus-specified as well as host-encoded proteins, transcribes and replicates the MV genome sequences (42).

Prior to International application PCT/US97/16718, the entire nucleotide sequences (only for the Edmonston B laboratory strain and the AIK-C vaccine strain), coding potential, and organization of the MV genome had been reported (34). The six virion structural proteins are encoded by six contiguous, non-overlapping genes which are arrayed as follows: 3'-N-P-M-F-H-L-5'. Two additional MV gene products of as yet uncertain function have also been identified. These two nonstructural proteins, known as C (approximately 20 kD) and V (approximately 45 kD), are both encoded by the P gene, the former by a second reading frame within the P mRNA; the latter by a cotranscriptionally edited P gene-derived mRNA which encodes a hybrid protein having the amino terminal sequences of P and a new zinc finger-like cysteine-rich carboxy terminal domain (16).

- 24 -

In addition to the sequences encoding the virus-specified proteins, the MV genome contains distinctive non-protein coding domains resembling those directing the transcriptional and replicative pathways of related viruses (16,43). These regulatory signals lie at the 3' and 5' ends of the MV genome and in short internal regions spanning each intercistronic boundary. The former encode the putative promoter and/or regulatory sequence elements directing genomic transcription, genome and antigenome encapsidation, and replication. The latter signal transcription termination and polyadenylation of each monocistronic viral mRNA and then reinitiation of transcription of the next gene. In general, the MV polymerase complex appears to respond to these signals much as the RNA-dependent RNA polymerases of other non-segmented negative strand RNA viruses (16,43,44,45).

Transcription initiates at or near the 3' end of the MV genome and then proceeds in a 5' direction producing monocistronic mRNAs (41,43,46). As the polymerase traverses the MV genomic template, it encounters putative stop/start signals which, in 3' to 5' order, are: a semi-conserved transcription termination/polyadenylation signal (A/G U/C UA A/U NN A_n, where N may be any of the four bases) at which each monocistronic RNA is completed; a non-transcribed intergenic trinucleotide punctuation mark (CUU; except at the H:L boundary where it is CGU); and a semiconserved start signal for transcription initiation of the next gene (AGG A/G NN C/A A A/G G A/U, where N may be any of the four bases) (46,47). Since some polymerase complexes fail to reinitiate, the abundance of each MV mRNA diminishes in parallel with the distance of the encoding gene from the genomic 3' end. This mRNA gradient directly corresponds to the relative

- 25 -

abundance of each virus-specified protein. This indicates that MV protein expression is ultimately controlled at the transcriptional level (45).

5 The 3' and 5' MV genomic termini contain non-protein coding sequences with distinct parallels to the leader and trailer RNA encoding regions of VSV (43). Nucleotides 1-55 define the region between the genomic 3' terminus and the beginning of the N gene, while 37 additional nucleotides can be found between
10 the end of the L gene and the 5' terminus of the genome. However, unlike VSV, or even the *paramyxoviruses* Sendai and NDV, MV does not transcribe these terminal regions into short, unmodified (+) or (-) sense leader RNAs (48,49,50). Instead, leader
15 readthrough transcripts, including full-length polyadenylated leader:N, leader:N:P, leader:N:P:M, and of course full-length antigenome MV RNAs are transcribed (49,50). Thus, the short leader transcript, the key operational element determining the
20 switch from transcription to replication of the VSV single-stranded, negative polarity genome (51,52,53), seems absent in MV. This leads to consideration and exploration of alternative models for this crucial reproductive event (43).

25 Measles virus, as well as all other Mononegavirales except the rhabdoviruses, appears to have extended its terminal regulatory domains beyond the confines of leader and trailer encoding sequences (43). For measles, these regions encompass the 107 3'
30 genomic nucleotides (the "3' genomic promoter region", also referred to as the "extended promoter", which comprises 52 nucleotides encoding the leader region, followed by three intergenic nucleotides, and 52 nucleotides encoding the 5' untranslated region of N
35 mRNA) and the 109 5' end nucleotides (69 encoding the

- 26 -

3' untranslated region of L mRNA, the intergenic trinucleotide and 37 nucleotides encoding the trailer). Within these 3' terminal approximately 100 nucleotides of both the genome and antigenome are two short regions of shared nucleotide sequence: 14 of 16 nucleotides at the absolute 3' ends of the genome and antigenome are identical. Internal to those termini, an additional region of 12 nucleotides of absolute sequence identity have been located. Their position at and near the sites at which the transcription of the MV genome must initiate and replication of the antigenome must begin, suggests that these short unique sequence domains encompass an extended promoter region.

These discrete sequence elements may dictate alternative sites of transcription initiation -- the internal domain mandating transcription initiation at the N gene start site, and the 3' terminal domain directing antigenome production (43,49,54). In addition to their regulatory role as cis-acting determinants of transcription and replication, these 3' extended genomic and antigenomic promoter regions encode the nascent 5' ends of antigenome and genome RNAs, respectively. Within these nascent RNAs reside as yet unidentified signals for N protein nucleation, another key regulatory element required for nucleocapsid template formation and consequently for amplification of transcription and replication. Figure 2 schematically shows the location and sequence of these highly conserved, putative cis-acting regulatory domains.

Terminal non-protein coding regions similar in location, size and spacing are present in the genomes of other members of the genus *Paramyxoviridae*, though only 8-11 of their absolute terminal nucleotides are shared by MV (43,55). The genomic termini of the

- 27 -

Morbillivirus canine distemper virus (CDV) displays a greater degree of homology with its MV relative: 73% of the nucleotides of the leader and trailer sequences of these two viruses are identical, including 16 of 18 at the absolute 3' termini and 17 of 18 at their 5' ends (56). No accessory internal CDV genomic domain-sharing homology to that of the MV extended promoter has been found. However, there is a 20 nucleotide long stretch lying between CDV genomic nucleotides 85 and 104 and 15,587 and 15,606 in which 15 of the 20 nucleotides are complementary (Gene Bank accession number AF 14953). This indicates that CDV, like MV contains an additional region within its non-coding 3' genomic and antigenomic ends that may provide important cis-acting promoter and/or regulatory signals (56).

Additionally, the precise length of the 3'-leader region (55 nucleotides) is identical among several members of the Family Paramyxoviridae (MV, CDV, PIV-3, BPV-3, SV and NDV). Further evidence for the importance of these extended, non-protein coding regions comes from analyses of a large number of distinct copy-back Defective Interfering genomes (DIs) recently cloned from subacute sclerosing panencephalitis (SSPE) brain tissue. No DI with a stem shorter than the 95 5' terminal genomic nucleotides was found. This indicates that the minimal signals needed for MV DI RNA replication and encapsidation extend well beyond the 37 nucleotide long trailer sequence to encompass the additional internal putative regulatory domain (57).

In all Paramyxoviruses, the cis-acting signals required for essential viral functions, including replication, transcription and encapsidation are contained in the non-coding genomic termini. The obligatory trans-acting elements for functionality are

- 28 -

contained in the N, P and L genes. Mutations in any of these regions may result in alteration of vital functions, including attenuation of viral transcription/replication efficiency.

5 The attenuation potential in the cis-acting sequence elements and in the trans-acting protein genes has been demonstrated in several viral systems by sequence analysis of their genomes (58,59).

10 The measles embodiment of this invention involved an analysis of the nucleotide sequences of the progenitor Edmonston wild-type MV isolate, together with available measles vaccine strains derived from this isolate (see Figure 1). Independent other wild-type isolates were examined for comparative purposes as well. In particular, the emphasis was on regions other than the 3' genomic promoter region and the L gene; those regions were the focus of International application PCT/US97/16718.

20 The nucleotide sequences (in positive strand, antigenomic, message sense) of four wild-type and five vaccine measles strains are set forth as follows with reference to the appropriate SEQ ID NOS. contained herein:

25	<u>Virus</u>	<u>Nucleotide Sequence</u>
	<u>Wild-Type</u>	
	Edmonston	SEQ ID NO:1
	1977	SEQ ID NO:2
	1983	SEQ ID NO:3
30	Montefiore	SEQ ID NO:4
	<u>Vaccine</u>	
	Rubeovax™	SEQ ID NO:5
	Moraten	SEQ ID NO:6
35	Zagreb	SEQ ID NO:7

- 29 -

AIK-C

SEQ ID NO:8

Each measles virus genome listed above is 15,894 nucleotides in length. Translation of the N gene starts with the codon at nucleotides 108-110; the translation stop codon is at nucleotides 1683-1685. The translated N protein is 525 amino acids long. Translation of the P gene starts with the codon at nucleotides 1807-1809; the translation stop codon is at nucleotides 3328-3330. The translated P protein is 506 amino acids long. Translation of the C gene starts with the codon at nucleotides 1829-1831; the translation stop codon is at nucleotides 2387-2389. The translated C protein is 189 amino acids long. Translation of the F gene starts with the codon at nucleotides 5449-5451; the translation stop codon is at nucleotides 7108-7110. The translated F protein is 553 amino acids long. The F gene stop/polyadenylation signal includes an eleven nucleotide gene-end signal at nucleotides 7237-7247, followed by an intergenic region at nucleotides 7248-7250 and the H gene-start signal at nucleotides 7251-7260.

Note that nucleotide 2499 of 1983 wild-type measles virus is indicated as "G" in SEQ ID NO:3. In fact, the base is actually a mixture of "G" and "C". Also note that nucleotide 2143 of Rubeovax™ vaccine virus is indicated as "T" in SEQ ID NO:5. In nine clones sequenced, this base was "T" in seven and "C" in two; thus, this base can be "T" or "C".

In addition, the Schwarz vaccine virus genome is identical to that of the Moraten vaccine virus genome (SEQ ID NO:6).

An analysis of the coding and noncoding (intercistronic) regions of the MV genome was carried out. Nucleotide and amino acid differences

- 30 -

distinguishing the N, P and C gene and protein sequences, and nucleotide differences distinguishing the F gene-end signal in the F/H intercistronic region of the Edmonston wild-type isolate, vaccine strains and
5 other independently isolated wild-type viruses were compared and aligned (see Tables 3-5 in Example 1 below).

As shown in Table 3, there are five nucleotide changes in the N genes of MV vaccine strains
10 compared to the progenitor Edmonston wild-type isolate. Two of these changes, at nucleotides 275 and 623, were conservative changes which did not result in changes to the amino acid sequence. Three changes, at nucleotides 492, 550 and 1542, resulted in changes to the amino
15 acid sequence of certain of the vaccine strains: (1) a change from a "C" to an "A" at nucleotide 492 resulted in a mutation from glutamine to lysine at amino acid 129 for the AIK-C vaccine strain; (2) a change from an "A" to a "G" at nucleotide 550 resulted
20 in a mutation from glutamic acid to glycine at amino acid 148 for the Moraten and Schwarz vaccine strains; and (3) a change from a "T" to an "A" at nucleotide 1542 resulted in a mutation from serine to threonine at amino acid 479 for the Rubeovax™, Moraten and Schwarz
25 vaccine strains. Because none of these three mutations were present in any of the later wild-type isolates, these three N gene mutations are potentially attenuating in the vaccine strains.

Without being bound by theory, the
30 attenuating phenotype of these three N gene mutations may be based upon the following discussion. The N protein must serve a number of functions in the measles virus life cycle. It must be able to interact with the viral genomic RNA and other copies of N to form the
35 nucleocapsid complex in which the MV genome is always

- 31 -

found. It interacts with the polymerase complex to allow transcription and replication. It has also been found to interact with the P protein separate from the replication complex. All of these functions could be points at which mutations might result in attenuation by affecting replicational efficiency of the virus.

Based on the deletion analysis of Bankamp et al. (60), the changes observed in the Edmonston vaccine lineage fall into areas that affect the functionality of the N protein as outlined below:

(1) Changes at amino acid 129 (glutamine to lysine in AIK-C) and amino acid 148 (glutamic acid to glycine in Moraten and Schwarz) both fall into a region necessary for the interaction of N and P proteins in solution. This interaction helps to keep the N protein from aggregating in a non-nucleocapsid specific manner. The P protein is also thought to serve as a chaperone, delivering N protein to the replicating genome for use in encapsidation. In Sendai virus, the first 400 amino acids comprise a domain that is also involved in the ability to encapsidate RNA, suggesting that at least some part of this region interacts with the RNA.

(2) The change at amino acid 479 (serine to threonine in Rubeovax™, Moraten, and Schwarz) falls within an area, that when deleted results in the formation of unstructured aggregates; this suggests it is an area of N:N interaction. This carboxy-terminal region of the N protein has also been shown in Sendai virus to interact with the P protein when assembled in nucleocapsids. In addition, the sequence from amino acid 400 to the carboxy-terminus (amino acid 525) shows a noticeably higher level of variation among wild-type MV N proteins compared to the rest of the protein.

As shown in Table 4, there are three nucleotide change in the P gene and three nucleotide

- 32 -

changes in the C gene of MV vaccine strains compared to the progenitor Edmonston wild-type isolate. The first change in the P gene, from "A" to "G" at nucleotide 2480, resulted in a mutation from glutamic acid to glycine at amino acid 225 for all vaccine strains; however, this change was not present in any of the later wild-type isolates. This unique mutation in the P protein is in one of the less conserved Morbillivirus amino acids: It is glutamic acid in both the wild-type and vaccine strains of the rinderpest virus, and cysteine in the canine distemper and phocine distemper virus strains (58). However, because this unique mutation is common to all the MV vaccine strains examined, but was not present in the later wild-type isolates, it is viewed as a potentially attenuating mutation.

The P and V mRNAs share the same start codon and the first 231 amino acids of the P and V proteins are identical. The V mRNA has an extra "G" between nucleotides 2498 and 2499 of the P mRNA. Editing takes place during transcription when an extra non-template-directed "G" residue is inserted between nucleotides 2498 and 2499, causing a shift in the reading frame, whereby the carboxy-terminal 276 amino acids of the P protein are replaced with a 68 amino acid cysteine-rich carboxy-terminus of the V protein. However, the mutation encoding amino acid 225 is located before the extra "G", so that mutation is potentially attenuating for both the P and the V proteins. At the present time, the function of the V protein is not known.

The second change in the P gene, from "G" to "A" at nucleotide 2630, resulted in a mutation from cysteine to tyrosine at amino acid 275. The third change in the P gene, from "T" to "C" at nucleotide 3122, resulted in a mutation from leucine to proline at

- 33 -

amino acid 439. These two mutations were unique to the AIK-C vaccine strain -- they were not present in the other vaccine strains or in any of the wild-type isolates -- and, therefore, they are viewed as potentially attenuating.

The first change in the C gene, from "C" to "T" at nucleotide 2046, resulted in a mutation from alanine to valine at amino acid 73 for all later wild-type isolates, as well as for all vaccine strains. Because of the presence of this mutation in the vaccine strains, but not in the progenitor wild-type strain, this mutation is viewed as potentially attenuating.

The next change in the C gene, from "T" to "C" at nucleotide 2139, resulted in a mutation from methionine to threonine at amino acid 104 for the Rubeovax™, Moraten and Schwarz vaccine strains. Because this mutation was not present in any of the later wild-type isolates, this C gene mutation is potentially attenuating in the vaccine strains.

The third change in the C gene, from "C" to "A" at nucleotide 2229, resulted in a mutation from serine to tyrosine at amino acid 134. This mutation was unique to the AIK-C vaccine strain -- it is not present in the other vaccine strains or in any of the other wild-type strains -- and, therefore, it is viewed as potentially attenuating.

The regions comprising the cis-acting elements which control transcription initiation and termination for each MV gene were found to be highly conserved among all measles viruses examined. With one exception, the sequences of the gene-start and gene-end signals were identical for all the viruses analyzed.

However, as shown in Table 5, there was one mutation in the F gene-end signal which spans nucleotides 7237-7247 (in antigenomic, message sense)

- 34 -

in two of the vaccine strains -- Moraten and Schwarz -- compared to the progenitor wild-type MV isolate, other derivative vaccine strains and other wild-type isolates: At nucleotide position 7243, Moraten and Schwarz had a "A", whereas the wild-type isolates and the other vaccine strains had a "T".

This F gene-end signal mutation is thought to affect the efficiency of transcription termination, which in turn could affect the levels of F gene expression, as well as downstream H gene expression. Decreases in F and H gene expression potentially are partially responsible for attenuation of the Moraten and Schwarz vaccine strains. This is consistent with the suggestion that a decrease in MV F gene expression may be a factor in attenuation (61). The importance of mutations in gene-start and gene-end signals was exemplified by the observation that a change in the RSV M2 gene-start signal had a profound attenuating effect on the virus and was associated with the *ts* phenotype of the virus (62).

Based on Table 3 and the foregoing discussion, the key attenuating sites for the MV N protein are as follows: amino acid residues 129 (glutamine → lysine), 148 (glutamic acid → glycine) and 479 (serine → threonine). Based on Table 4 and the foregoing discussion, the key attenuating sites for the P and C proteins are as follows: amino acid residues 225 (glutamic acid → glycine), 275 (cysteine → tyrosine) and 439 (leucine → proline) for the P protein and amino acid residues 73 (alanine → valine), 104 (methionine → threonine) and 134 (serine → tyrosine) for the C protein.

It is understood that the nucleotide changes responsible for these amino acid changes are not limited to those set forth in Tables 3 and 4 of Example

- 35 -

1 below; all changes in nucleotides which result in codons which are translated into these amino acids are within the scope of this invention.

5 In addition, based on Table 5 and the foregoing discussion, the key attenuating mutation for the F gene-end signal is nucleotide 7243 (T → C) (in antigenomic, message sense).

10 In a further embodiment of this invention, the measles virus phenotype is further attenuated by combining one or more of the above-referenced N, P or C gene or F gene-end signal mutations with one or more of each of the coordinate 3' genomic promoter region and L gene mutations described in International application PCT/US97/16718, which are as follows: for the MV 3' genomic promoter region, the mutations are nucleotide 15 26 (A → T), nucleotide 42 (A → T or A → C) and nucleotide 96 (G → A) (in antigenomic, message sense), while for the L protein the mutations are amino acid residues 331 (isoleucine → threonine), 1409 (alanine → threonine), 1624 (threonine → alanine), 1649 20 (arginine → methionine), 1717 (aspartic acid → alanine), 1936 (histidine → tyrosine), 2074 (glutamine → arginine) and 2114 (arginine → lysine). Again, it is understood that all changes in nucleotides 25 which result in codons which are translated into these amino acids are within the scope of this invention.

Human respiratory syncytial virus (RSV) is another nonsegmented, negative-sense, single stranded enveloped RNA virus. RSV belongs to the Subfamily 30 Pneumovirinae and the genus *Pneumovirus* (see Table 1).

Two major subgroups of human RSV, designated A and B, have been identified based on reactivities of the F and G surface glycoproteins with monoclonal antibodies (63). More recently, the A and B lineages

- 36 -

of RSV strains have been confirmed by sequence analysis (64,65). Bovine, ovine, and caprine strains of this virus have also been isolated. The host specificity of the virus is most clearly associated with the G attachment protein, which is highly divergent between the human and the bovine/ovine strains (66,67), and may be influenced, at least in part, by receptor binding.

RSV is the primary cause of serious viral pneumonia and bronchiolitis in infants and young children. Serious disease, i.e., lower respiratory tract disease (LRD), is most prevalent in infants less than six months of age. It most commonly occurs in the nonimmune infant's first exposure to RSV. RSV additionally is associated with asthma and hyperreactive airways and it is a significant cause of mortality in "high risk" children with bronchopulmonary dysplasia and congenital heart disease (CHD). It is also one of the common viral respiratory infections predisposing to otitis media in children. In adults, RSV generally presents as uncomplicated upper respiratory illness; however, in the elderly it rivals influenza as a predisposing factor in the development of serious LRD, particularly bacterial bronchitis and pneumonia. Disease is always confined to the respiratory tract, except in the severely immunocompromised, where dissemination to other organs can occur. Virus is spread to others by fomites contaminated with virus-containing respiratory secretions, and infection initiates through the nasal, oral, or conjunctival mucosa.

RSV disease is seasonal and virus is usually isolated only in the winter months, e.g., from November to April in northern latitudes. The virus is ubiquitous, and over 90% of children have been infected at least once by 2 years of age. Multiple strains

- 37 -

cocirculate. There is no direct evidence of antigenic drift (such as that seen with influenza A viruses), but sequence studies demonstrating accumulation of amino acid changes in the hypervariable regions of the G protein and SH proteins suggest that immune pressure
5 may drive virus evolution.

In mouse and cotton rat models, both the F and G proteins of RSV elicit neutralizing antibodies and immunization with these proteins alone provides
10 longterm protection against reinfection (68,69).

In humans, complete immunity to RSV does not develop and reinfections occur throughout life (70,71); however, there is evidence that immune factors will protect against severe disease. A decrease in severity
15 of disease is associated with two or more prior infections and there is evidence that children infected with one of the two major RSV subgroups may be somewhat protected against reinfection with the homologous subgroup (72), observations which suggest that a live
20 attenuated virus vaccine may provide protection sufficient to prevent serious morbidity and mortality. Infection with RSV elicits both antibody and cell mediated immunity. Serum neutralizing antibody to the F and G proteins has been associated, in some studies,
25 with protection from LRD, although reduction in upper respiratory disease (URD) has not been demonstrated. High levels of serum antibody in infants is associated with protection against LRD, and administration of intravenous immunoglobulin with high RSV neutralizing
30 antibody titers has been shown to protect against severe disease in high risk children (71,73,74). The role of local immunity, and nasal antibody in particular, is being investigated.

The RSV virion consists of a
35 ribonucleoprotein core contained within a lipoprotein

- 38 -

envelope. The virions of pneumoviruses are similar in size and shape to those of all other paramyxoviruses. When visualized by negative staining and electron microscopy, virions are irregular in shape and range in diameter from 150-300 nm (75). The nucleocapsid of this virus is a symmetrical helix similar to that of other paramyxoviruses, except that the helical diameter is 12-15 nm rather than 18nm. The envelope consists of a lipid bilayer that is derived from the host membrane and contains virally coded transmembrane surface glycoproteins. The viral glycoproteins mediate attachment and penetration and are organized separately into virion spikes. All members of the paramyxovirus subfamily have hemagglutinating activity, but this function is not a defining feature for pneumoviruses, being absent in RSV but present in Pneumovirus of mice (PVM) (76). Neuraminidase activity is present in members of the genera Paramyxovirus, Rubulavirus, and is absent in Morbillivirus and Pneumovirus (76).

RSV possesses two subgroups, designated A and B. The wild-type RSV (strain 2B) genome is a single strand of negative-sense RNA of 15,218 nucleotides (SEQ ID NO:9) that are transcribed into ten major subgenomic mRNAs which encode eleven gene products. Each of the ten mRNAs encodes a major polypeptide chain: Three are transmembrane surface proteins (G, F and SH); three are the proteins associated with genomic RNA to form the viral nucleocapsid (N, P and L); two are nonstructural proteins (NS1 and NS2) which accumulate in the infected cells but are also present in the virion in trace amounts and may play a role in regulating transcription and replication; one is the nonglycosylated virion matrix protein (M); and the last is M2, another nonglycosylated protein recently shown to be an RSV-specified transcription elongation factor (see Figure

- 39 -

3) (another gene product is also encoded by the M2 gene). These ten viral proteins account for nearly all of the viral coding capacity.

5 The viral genome is encapsidated with the major nucleocapsid protein (N), and is associated with the phosphoprotein (P), and the large (L) polymerase protein. These three proteins have been shown to be necessary and sufficient for directing RNA replication of cDNA encoded RSV minigenomes (77). Further studies
10 have shown that for transcription to proceed with full processing, the M2 protein (ORF 1) is required (75). When the M2 protein is missing, truncated transcripts predominate, and rescue of the full length genome does not occur (75).

15 Both the M (matrix protein) and the M2 proteins are internal virion-associated proteins that are not present in the nucleocapsid structure. By analogy with other nonsegmented negative-stranded RNA viruses, the M protein is thought to render the
20 nucleocapsid transcriptionally inactive before packaging and to mediate its association with the viral envelope. The NS1 and NS2 proteins have only been detected in very small amounts in purified virions, and at this time are considered non-structural. Their
25 functions are uncertain, though they may be regulators of transcription and replication. Three transmembrane surface glycoproteins are present in virions: G, F, and SH. G and F (fusion) are envelope glycoproteins that are known to mediate attachment and penetration of the
30 virus into the host cell. In addition, these glycoproteins represent major independent immunogens (78). The function of the SH protein is unknown, although a recent report has implicated its involvement in the fusion function of the virus (79).

- 40 -

As discussed below, the genomes of two wild-type RSV subgroup B strains (2B and 18537) were sequenced in their entirety, as described in International application PCT/US9716718 (see SEQ ID NOS:9 and 10). Genomic RNA is neither capped nor polyadenylated (80). In both the virion and intracellularly, genomic RNA is tightly associated with the N protein.

The 3' end of the genomic RNA consists of a 44-nucleotide extragenic leader region that is presumed to contain the major viral promoter (Fig. 3). The 3' genomic promoter region is followed by ten viral genes in the order 3'-NS1-NS2-N-P-M-SH-G-F-M2-L-5' (Fig. 3). The L gene is followed by a 145-149 nucleotide extragenic trailer region (see Figure 3). Each gene begins with a conserved nine-nucleotide gene start signal 3'-GGGGCAAAU (except for the ten-nucleotide gene start signal of the L gene, which is 3'-GGGACAAAAU; and the gene start signal of the SH gene for 2B and 18537, which is 3'-GGGGUAAAAU; differences underlined). For each gene, transcription begins at the first nucleotide of the signal. Each gene terminates with a semi-conserved 12-14 nucleotide gene end (3'-A G U/G U/A ANNN U/A A_{3,5}) (where N can be any of the four bases) that directs transcription termination and polyadenylation (Fig. 3). The first nine genes are non-overlapping and are separated by intergenic regions that range in size from 3 to 56 nucleotides for RSV B strains (Fig. 3). The intergenic regions do not contain any conserved motifs or any obvious features of secondary structure and have been shown to have no influence on the preceding and succeeding gene expression in a minireplicon system (Fig. 3). The last two RSV genes overlap by 68 nucleotides (Fig. 3). The gene-start signal of the L gene is located inside of,

- 41 -

rather than after, the M2 gene. This 68 nucleotide overlap sequence encodes the last 68 nucleotides of the M2 mRNA (exclusive of the Poly-A tail), as well as the first 68 nucleotides of the L mRNA.

5 Ten different species of subgenomic polyadenylated mRNAs and a number of polycistronic polyadenylated read-through transcripts are the products of genomic transcription (75).
10 Transcriptional mapping studies using UV light mediated genomic inactivation showed that RSV genes are transcribed in their 3' to 5' order from a single promoter near the 3' end (81). Thus, RSV synthesis appears to follow the single entry, sequential transcription model proposed for all Mononegavirales
15 (16,82). According to this model, the polymerase (L) contacts genomic RNA in the nucleocapsid form at the 3' genomic promoter region and begins transcription at the first nucleotide. RSV mRNAs are co-linear copies of the genes, with no evidence of mRNA editing or
20 splicing.

 Sequence analysis of intracellular RSV mRNAs showed that synthesis of each transcript begins at the first nucleotide of the gene start signal (75). The 5' end of the mRNAs are capped with the structure
25 m⁷G(5')ppp(5')Gp (where the underlined G is the first template nucleotide of the mRNA) and the mRNAs are polyadenylated at their 3' ends (83). Both of these modifications are thought to be made co-transcriptionally by the viral polymerase. Three
30 regions of the RSV 3' genomic promoter have been found to be important as cis acting elements (84). These regions are the first ten nucleotides (presumably acting as a promoter), nucleotides 21-25, and the gene start signal located at nucleotides 45-53 (84). Unlike
35 other Paramyxovirinae, such as measles, Sendai and PIV-

- 42 -

3, the remainder of the leader and non-coding region of NS1 gene of RSV was found to be highly tolerant of insertions, deletions and substitutions (84).

5 Additionally, by saturation mutagenesis
(wherein each base is replaced independently by each of the other three bases and compared for translation and replication efficiencies) within the first 12 nucleotides of the 3' genomic promoter region, a U-tract located at nucleotides 6-10 was shown to be quite
10 intolerant of substitutions (84). In contrast, the first five nucleotides were relatively tolerant of a number of substitutions and two of them at position four were up-regulatory mutations, resulting in a four- to 20-fold increase in RSV-CAT RNA replication and
15 transcription. Using a bi-cistronic minireplicon system, gene-start and gene-end motifs were shown to be signals for mRNA synthesis and appear to be self-contained and largely independent of the nature of adjoining sequence (85).

20 The L gene start signal lies 68 nucleotides upstream of the M2 gene-end signal, resulting in gene overlap (Fig. 3) (75). The presence of the M2 gene-end signal within the L gene results in a high frequency of premature termination of L gene transcripts. Full
25 length L mRNA is much less abundant and is made when the polymerase fails to recognize the M2 gene-end motif. This results in much lower transcription of L mRNA. The gene overlap seems incompatible with a model of linear sequential transcription. It is not known
30 whether the polymerase that exits the M2 gene jumps backward to the L gene-start signal or whether there is a second, internal promoter for L gene transcription (75). It is also possible that the L gene is accessible by a small fraction of polymerases that fail

- 43 -

to start transcription at the M2 gene-start signal and slide down the M2 gene to the L gene-start signal.

5 The relative abundance of each RSV mRNA decreases with the distance of its gene from the promoter, presumably due to polymerase fall-off during sequential transcription (81). Gene overlap is a second mechanism that reduces the synthesis of full length L mRNA. Also, certain mRNAs have features that might reduce the efficiency of translation. The
10 initiation codon for SH mRNA is in a suboptimal Kozak sequence context, while the G ORF begins at the second methionyl codon in the mRNA.

RSV RNA replication is thought (75) to follow the model proposed from studies with vesicular
15 stomatitis virus and Sendai virus (16,82). This involves a switch from the stop-start mode of mRNA synthesis to an antiterminator read-through, the latter resulting in synthesis of positive sense replication-intermediate (RI) RNA that is an exact complementary
20 copy of genomic RNA. This serves in turn as the template for the synthesis of progeny genomes. The mechanism involved in the switch to the antiterminator mode is proposed to involve cotranscriptional encapsidation of the nascent RNA by N protein (16,82).
25 RNA replication in RSV like other nonsegmented negative-strand RNA viruses is dependent on ongoing protein synthesis (86). Predicted RI RNA has been detected for the standard virus as well as RSV-CAT minigenome (75,86). RI RNA was 10-20 fold less
30 abundant intracellularly than was the progeny genome both for the standard and the minigenome system.

The RSV subgroup B embodiment of this invention involved an analysis of the nucleotide sequences of various wild-type, vaccine and revertant
35 RSV strains. In particular, the emphasis was on

- 44 -

regions other than the 3' genomic promoter region and the L gene; those regions were the focus of International application PCT/US97/16718.

5 The nucleotide sequences (in positive strand, antigenomic, message sense) of various wild-type, vaccine and revertant RSV subgroup B strains are set forth as follows with reference to the appropriate SEQ ID NOS. contained herein:

10	<u>Virus</u>	<u>Nucleotide Sequence</u>	<u>Genome</u>
	<u>Wild-Type</u>		<u>Length</u>
	2B	SEQ ID NO:9	15218
	18537	SEQ ID NO:10	15229
15	<u>Vaccine</u>		
	2B33F	SEQ ID NO:11	15219
	2B20L	SEQ ID NO:12	15219
	<u>Revertant</u>		
20	2B33F TS(+)	SEQ ID NO:13	15219
	2B20L TS(+)	SEQ ID NO:14	15219

25 Translation of the M gene starts with the codon at nucleotides 3262-3264; the translation stop codon is at nucleotides 4030-4032. The translated M protein is 256 amino acids long. The M gene stop/polyadenylation signal includes a twelve nucleotide gene-end signal at nucleotides 4196-4207, followed by an intergenic region at nucleotides 4208-

30 4216 and the SH gene-start signal at nucleotides 4217-4225.

35 An analysis of the coding and noncoding (intercistronic) regions of the RSV subgroup B genome was carried out. Nucleotide and amino acid differences distinguishing the SH gene and protein sequences, and

- 45 -

nucleotide differences distinguishing the M gene-end signal in the M/SH intercistronic region of various wild-type, vaccine and revertant RSV strains were carried out (see Tables 6, 7 and 9 in Example 2 below).

5 The regions comprising the cis-acting elements which control transcription termination for each gene were found to be highly conserved among all RSV subgroup B viruses examined. With one exception, the sequences of the gene-start and gene-end signals
10 were identical for all the viruses analyzed. The third nucleotide of the M gene-end signal of the wild-type 2B, vaccine 2B33F and revertant 2B33F TS(+) strains was a G, while the third nucleotide of all other RSV subgroup B gene-end signals was a T.

15 More importantly, as shown in Table 7, there was one mutation in the M gene-end signal which spans nucleotides 4196-4207 in the wild-type 2B virus (in antigenomic, message sense) and spans nucleotides 4197-4208 in the 2B33F vaccine strain and the 2B33F TS(+) revertant strain: At nucleotide position 4199, wild-type 2B virus had a "T", whereas the 2B33F and 2B33F
20 TS(+) strains had a "C" in the corresponding nucleotide position 4200 (these strains have an extra nucleotide in their 3' genomic promoter regions). This mutation
25 was not present in any of the 18537 wild-type strain, the 2B20L vaccine strain or its TS(+) revertant strain.

 As shown in Table 11 and Figures 4-6, the sequence of the M gene-end signal impacts SH gene expression. The RSV subgroup B 2B33F mutant and its
30 TS(+) revertant have this unique nucleotide at this fourth position of the M gene-end signal (at nucleotide 4200 in the mutant and revertant) that is not found in their 2B parental strain (at nucleotide 4199) or in any of the other RSV subgroup B or A viruses analyzed.

- 46 -

As shown by Northern blot analyses (Figures 4 and 6) and a ribonuclease protection assay (Figure 5) which are discussed in Example 2 below, the wild-type 2B strain produced a slight excess of bicistronic M:SH over monocistronic M transcripts. In contrast the 2B33F mutant and its 2B33F TS(+) revertant produced practically no monocistronic M and SH transcripts; instead, the bulk of their transcription products were bicistronic and higher molecular weight read-through transcripts. These bicistronic and read-through transcripts are likely to be constrained in their ability to translate the SH gene product. Thus, the strains containing this mutation have down-regulated SH expression compared to the 2B parental strain, and have essentially stopped producing the SH protein. This shift to the predominance of bicistronic transcription products and the concomitant down-regulation of the downstream gene product, SH, provides evidence that the mutation in the M gene-end signal contributes to the attenuation phenotype of these two strains.

Therefore, based on Tables 6-11, Figures 4-6 and the foregoing discussion, the key attenuating mutation for the M gene-end signal is nucleotide 4199 (T → C) (in antigenomic, message sense).

It is interesting to note that the SH gene of the 2B33F mutant is blistered with nucleotide changes (biased hypermutation) compared to that of the 2B parent (see Table 6), some of which would result in amino acid substitutions in the SH protein. One change at nucleotide 4498 of 2B33F converts the predicted SH translation stop codon to glutamine. This results in a predicted length for the 2B33F SH protein that is substantially longer than that of the 2B parent.

In a further embodiment of this invention, the RSV subgroup B phenotype is further attenuated by

- 47 -

combining the above-referenced M gene-end signal mutation with one or more of each of the coordinate 3' genomic promoter region and L gene mutations described in International application PCT/US97/16718, which are as follows: for the RSV subgroup B 3' genomic promoter region, the mutations are nucleotide 4 (C → G), and the insertion of an additional A in the stretch of A's at nucleotides 6-11 (in antigenomic message sense), while for the L protein the mutations are amino acid residues 353 (arginine → lysine), 451 (lysine → arginine), 1229 (aspartic acid → asparagine), 2029 (threonine → isoleucine) and 2050 (asparagine → aspartic acid). Again, it is understood that all changes in nucleotides which result in codons which are translated into these amino acids are within the scope of this invention.

When the 3' genomic promoter region is modified by the insertion of an additional A in the stretch of A's at nucleotides 6-11, it is understood that the attenuating mutation in the M gene-end signal will be at nucleotide 4200, rather than nucleotide 4199.

The attenuated viruses of this invention exhibit a substantial reduction of virulence compared to wild-type viruses which infect human and animal hosts. The extent of attenuation is such that symptoms of infection will not arise in most immunized individuals, but the virus will retain sufficient replication competence to be infectious in and elicit the desired immune response profile in the vaccinee.

The attenuated viruses of this invention may be used to formulate a vaccine. To do so, the attenuated virus is adjusted to an appropriate concentration and formulated with any suitable vaccine adjuvant, diluent or carrier. Physiologically

- 48 -

acceptable media may be used as carriers. These include, but are not limited to: an appropriate isotonic medium, phosphate buffered saline and the like. Suitable adjuvants include, but are not limited to MPL™ (3-O-deacylated monophosphoryl lipid A; RIBI ImmunoChem Research, Inc., Hamilton, MT) and IL-12 (Genetics Institute, Cambridge, MA).

In one embodiment of this invention, the formulation including the attenuated virus is intended for use as a vaccine. The attenuated virus may be mixed with cryoprotective additives or stabilizers such as proteins (e.g., albumin, gelatin), sugars (e.g., sucrose, lactose, sorbitol), amino acids (e.g., sodium glutamate), saline, or other protective agents. This mixture is maintained in a liquid state, or is then dessicated or lyophilized for transport and storage and mixed with water immediately prior to administration.

Formulations comprising the attenuated viruses of this invention are useful to immunize a human or animal subject to induce protection against infection by the wild-type counterpart of the attenuated virus. Thus, this invention further provides a method of immunizing a subject to induce protection against infection by an RNA virus of the Order Mononegavirales by administering to the subject an effective immunizing amount of a vaccine formulation incorporating an attenuated version of that virus as described hereinabove.

A sufficient amount of the vaccine in an appropriate number of doses must be administered to the subject to elicit an immune response. Persons skilled in the art will readily be able to determine such amounts and dosages. Administration may be by any conventional effective form, such as intranasally, parenterally, orally, or topically applied to any

- 49 -

mucosal surface such as intranasal, oral, eye, lung, vaginal or rectal surface, such as by an aerosol spray. The preferred means of administration is by intranasal administration.

5 In connection with International application PCT/US97/16718, samples of the Moraten measles virus vaccine strain were deposited by Applicants on August 21, 1997 with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, 10 U.S.A., under the provisions of the Budapest Treaty for the Deposit of Microorganisms for the Purposes of Patent Procedures ("Budapest Treaty") and have been assigned ATCC accession number VR2587, and samples of the 2B wild-type RSV virus were deposited by Applicants 15 on August 21, 1997 with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A., under the provisions of the Budapest Treaty and have been assigned ATCC accession number VR2586.

20 Given these two deposited strains and the sequence information for these and other strains provided herein, one can use site-directed mutagenesis and rescue techniques described above to introduce mutations (or restore a wild-type genotype) of all the 25 strains described herein, as well as taking these strains and making additional mutations from the panel of mutations set forth in Tables 3-11 below.

30 In order that this invention may be better understood, the following examples are set forth. The examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention.

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- 50 -

Examples

Standard molecular biology techniques are utilized according to the protocols described in Sambrook et al. (87).

Example 1Measles

Moraten MV vaccine virus was grown once, directly from the Attenuvax™ vaccine vial (Lot #0716B), the Schwarz vaccine virus was grown once (Lot 96G04/M179 G41D), while the Zagreb and Rubeovax™ vaccine viruses were each grown twice in the Vero cells before RNAs were made for sequence analysis. MV wildtype isolate Montefiore (57) was passed 5-6 times in Vero cells before extraction of RNA materials and similarly, MV wildtype isolates 1977, 1983 (14) were grown 5-7 times before extracting materials for analysis. Edmonston wild-type isolate received from Dr. J. Beeler (CBER) (see Fig. 1) was the original Edmonston isolate already passaged seven times in human kidney cells and three times in Vero cells before receipt and further passaged once in Vero cells before using for sequence analysis.

RNA was prepared by infecting Vero cells at a multiplicity of infection (m.o.i.) of 0.1 to 1.0 and allowed to reach maximum cytopathology before being harvested. Total RNA from measles virus-infected cells was extracted using Trizol™ reagent (Gibco-BRL).

The total RNA isolated from Vero cell passage material was amplified by the Reverse Transcriptase-PCR (Perkin-Elmer/Cetus) procedure using measles (Edmonston B strain (19)) specific primer pairs spanning the 3' and 5' promoter regions and the L gene of the viral

- 51 -

genome. Table 2 presents these primer sequences. The primers of SEQ ID NOS:15-34, 54, 57 and 58 are in antigenomic message sense. The primers of SEQ ID NOS:35-53, 55, 56 and 59 are in genomic negative-sense.

5

Table 2
Primers for PCR and Sequencing MV L Genes
and Genomic Termini

10

15

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25

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35

9047	CATATCACTCACTCTGGGATGGAG ₉₀₇₀	(SEQ ID NO:15)
9371	TCAGAACATCAAGCACCGCC ₉₃₉₀	(SEQ ID NO:16)
9741	ACAGTCAAGACTGAGATGAG ₉₇₆₀	(SEQ ID NO:17)
10001	AAGAGTCAGATACATGTGGA ₁₀₀₂₀	(SEQ ID NO:18)
10351	ACATGAATCAGCCTAAAGTC ₁₀₃₇₀	(SEQ ID NO:19)
10674	CCGAAAGAGTTCCTGCGTTACGACC ₁₀₆₉₈	(SEQ ID NO:20)
11083	CAGTCCACACAAGTACCAGG ₁₁₁₀₂	(SEQ ID NO:21)
11461	GTCAGAAGCTGTGGACCATC ₁₁₄₈₀	(SEQ ID NO:22)
11841	AATATTGCTACAACAATGGC ₁₁₈₆₀	(SEQ ID NO:23)
12196	ACTCTTCATTCTAGACTGG ₁₂₂₁₅	(SEQ ID NO:24)
12542	GTCCAATTATGACTATGAAC ₁₂₅₆₁	(SEQ ID NO:25)
12891	AGAACAGACATGAAGCTTGC ₁₂₉₁₀	(SEQ ID NO:26)
13232	CCAACAAGGAATGCTTCTAG ₁₃₂₅₁	(SEQ ID NO:27)
13551	ACAGCACTATCTATGATTGACCTGG ₁₃₅₇₅	(SEQ ID NO:28)
13930	GCAACATGGTTTACACATGC ₁₃₉₄₉	(SEQ ID NO:29)
14280	AGATTGAGAGTTGATCCAGG ₁₄₂₉₉	(SEQ ID NO:30)
14629	AGGAGATACTTAACTAAGC ₁₄₆₄₈	(SEQ ID NO:31)
14981	TAAGCTTATGCCTTTCAGCG ₁₅₀₀₀	(SEQ ID NO:32)
15337	TTAACGGACCTAAGCTGTGC ₁₅₃₅₆	(SEQ ID NO:33)
15671	GAAACAGATTATTATGACGG ₁₅₆₉₀	(SEQ ID NO:34)
9290	CGGGCTATCTAGGTGAACTTCAGG ₉₂₆₇	(SEQ ID NO:35)
9500	ATTTGGATATGGAATATGAG ₉₄₈₁	(SEQ ID NO:36)
9840	ACTCAACTGAACTACCACTG ₉₈₂₁	(SEQ ID NO:37)
10181	AAGAACATCATGTATTTTCAG ₁₀₁₆₂	(SEQ ID NO:38)

- 52 -

10549 TTATCAACGCACTGCTCATG₁₀₅₃₀ (SEQ ID NO:39)
 10919 ATTTTCAGCAATCACTTGGCATGCC₁₀₈₉₅ (SEQ ID NO:40)
 11280 GCCTCTGTGCAAACAAGCTG₁₁₂₆₁ (SEQ ID NO:41)
 11638 TCTCTAGTTACTCTAGCAGC₁₁₆₁₉ (SEQ ID NO:42)
 5 12010 AGGTCGTTGTTTGTGAGGAG₁₁₉₉₁ (SEQ ID NO:43)
 12361 TCGTCCTCTTCTTTACTGTC₁₂₃₄₂ (SEQ ID NO:44)
 12689 CCGTCCTCGAGCTAGCCTCG₁₂₆₇₀ (SEQ ID NO:45)
 13052 CTCCTCCAGGCTCACATTGG₁₃₀₃₃ (SEQ ID NO:46)
 13420 GGGTTGGTACATAGCTCTGC₁₃₄₀₁ (SEQ ID NO:47)
 10 13767 CACCCATCTGATATTTCCCTGATGG₁₃₇₄₃ (SEQ ID NO:48)
 14099 TGGTTGACAGTACAAATCTG₁₄₀₈₀ (SEQ ID NO:49)
 14460 CTGAAATGGGAAGATTGTGC₁₄₄₄₁ (SEQ ID NO:50)
 14820 AGCAATCTACACTGCCTACC₁₄₈₀₁ (SEQ ID NO:51)
 15180 TCACAGATGATTCAATTATC₁₅₁₆₁ (SEQ ID NO:52)
 15 15530 GATCCTAGATATAAGTTCTC₁₅₅₁₁ (SEQ ID NO:53)

 1 ACCAAACAAAGTTGGGTAAGG₂₁ (SEQ ID NO:54)
 GGGGGATCC₁₀₀ATCCCTAATCCTGCTCTTGTCCC₇₈ (SEQ ID NO:55)
 200 GATTCCTCTGATGGCTCCAC₁₈₁ (SEQ ID NO:56)
 20 15721 TAACAGTCAAGGAGACCAAAG₁₅₇₄₁ (SEQ ID NO:57)
 GGGGAAGCTT₁₅₈₀₁AACCCTAATCCTGCCCTAGGTGG₁₅₈₂₃ (SEQ ID NO:58)
 15894 ACCAGACAAAGCTGGGAATAGA₁₅₈₇₃ (SEQ ID NO:59)

25 Overlapping PCR fragments of the complete
 viral genome were directly sequenced without cloning to
 achieve the consensus sequence, by the dideoxy
 terminator cycle sequencing method using both strands
 (ABI PRISM 377 sequencer and ABI PRISM sequencing Kit).
 To determine the sequence at the absolute termini, a
 30 ligation procedure described previously was used (56).

The nucleotide sequences were determined for
 regions other than the genomic promoter region and the
 L gene of the progenitor Edmonston wild-type MV
 isolate, for the available vaccine strains derived from
 35 this isolate, as well as for other wild-type strains.

- 53 -

Significant nucleotide (in antigenomic, message sense) and amino acid differences were then compared and aligned as set forth in Tables 3-5 (differences are in *italics*):

5

Table 3

Differences in MV N Nucleotides and Amino Acids
Between Edmonston Wild-Type and Vaccine Strains

10

<u>Nucleotide</u>	<u>275</u>	<u>492</u>	<u>550</u>	<u>623</u>	<u>1542</u>
-------------------	------------	------------	------------	------------	-------------

Edmonston w-t	GTC	CAA	GAG	GCC	TCG
---------------	-----	-----	-----	-----	-----

Mutation	GTG	AAA	GGG	GCT	ACG
----------	-----	-----	-----	-----	-----

15

<u>Amino Acid</u>	<u>56</u>	<u>129</u>	<u>148</u>	<u>172</u>	<u>479</u>
-------------------	-----------	------------	------------	------------	------------

Edmonston w-t	V	Q	E	A	S
---------------	---	---	---	---	---

Rubeovax™ vac.	V	Q	E	A	T
----------------	---	---	---	---	---

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Moraten vac.	V	Q	G	A	T
--------------	---	---	---	---	---

Schwarz vac.	V	Q	G	A	T
--------------	---	---	---	---	---

Zagreb vac.	V	Q	E	A	S
-------------	---	---	---	---	---

AIK-C vac.	V	K	E	A	S
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- 54 -

Table 4
Differences in MV P and C Nucleotides and Amino Acids
Between Wild-Type and Vaccine Strains

<u>Gene</u>	<u>C</u>	<u>C</u>	<u>C</u>	<u>P*</u>	<u>P</u>	<u>P</u>
<u>Nucleotide</u>	<u>2046</u>	<u>2139</u>	<u>2229</u>	<u>2480</u>	<u>2630</u>	<u>3122</u>
Edmonston w-t	GCC	ATG	TCT	GAG	TGT	CTA
Mutation	GTC	ACG	TAT	GGG	TAT	CCA
<u>Amino Acid</u>	<u>73</u>	<u>104</u>	<u>134</u>	<u>225</u>	<u>275</u>	<u>439</u>
Edmonston w-t	A	M	S	E	C	L
1977 w-t	V	M	S	E	C	L
1983 w-t	V	M	S	E	C	L
Montefiore w-t	V	M	S	E	C	L
Rubeovax™ vac.	V	T	S	G	C	L
Moraten vac.	V	T	S	G	C	L
Schwarz vac.	V	T	S	G	C	L
Zagreb vac.	V	M	S	G	C	L
AIK-C vac.	V	M	Y	G	Y	P

* Identical change in V protein

- 55 -

Table 5
Differences in MV F Gene-End Signal Between
Edmonston Wild-Type and Vaccine Strains

Nucleotides 7237-7247

Edmonston w-t	G T T A A T T A A A A
Rubeovax™ vac.	G T T A A T T A A A A
Moraten vac.	G T T A A T C A A A A
Schwarz vac.	G T T A A T C A A A A
Zagreb vac.	G T T A A T T A A A A
AIK-C vac.	G T T A A T T A A A A

↑

7243

- 56 -

Example 2
RSV Subgroup B

5 The temperature-sensitive (*ts*) phenotype is
strongly associated with attenuation *in vivo*; in
addition, some non-*ts* mutations may also be
attenuating. Identification of *ts* and non-*ts*
attenuating mutations was achieved by sequence analysis
and evaluation of *ts*, cold-adapted (*ca*), and *in vivo*
10 growth phenotypes of RSV mutants and revertants.

 The genomes of the following three RSV 2B
strains have been completely sequenced: The 2B wild-
type parent, a *ts* and *ca* derivative thereof designated
2B33F and one *ts*(+) revertant designated 2B33F TS(+).
15 The 2B33F strain is described in U.S. Serial No.
08/059,444 (88), which is hereby incorporated by
reference. After identifying regions where mutations
in 2B33F are located, nine additional isolates of 2B33F
"revertants" obtained following *in vitro* passaging at
20 39°C and *in vivo* passaging in African green monkeys or
chimpanzees have been sequenced in those previously-
identified mutant regions. The *ts*, *ca*, and attenuation
phenotypes of many of these revertants have now been
characterized and assessed. Correlations between *ts*
25 phenotype, virus attenuation and sequence changes have
been identified.

 A summary of results is presented in Tables
6-11.

- 57 -

Table 6
Sequence comparison between RSV 2B and 2B33F strains

Gene/ region	Nucl. pos.†	Nucleotide changes			Amino acid changes
	3' end of vRNA	RSV 2B	RSV 2B33F	RSV 2B33F TS(+), 5a revertant	
Genomic Promoter	4 6	C -	G extra A	G extra A	non-coding non-coding
M	4175 4199	T T	C C	C C	non-coding non-coding
SH	4329 4409 4420 4442 4454 4484 4497 4505 4525 4526 4542 4561 4575 4598	T T T T T T T T T T T T T T	C C C C C C C C C C C C C C	C C C C C C C C C C C C C C	Phe-Leu (10) none Ile (36) Ile-Thr (40) none His (47) none Cys (51) none Tyr (61) Stop-Gln (66) none Ser (68) Ile-Thr (75) Ile-Thr (75) Stop-Gln (81) Leu-Pro (87) Trp-Arg (92) none Thr (99)
L	9559 9853* 12186 14587 15071	G A G C A	A G A T G	A A A T G	Arg-Lys (353) Lys-Arg (451)* Asp-Asn (1229) Thr-Ile (2029) non-coding

† For 2B33F and 2B33F TS(+), nucl. pos. numbers
are one larger than for 2B for M, SH & L genes

* At pos. 9853, the Lys-Arg change has reverted
back to Lys in the 2B33F TS(+) strain

- 58 -

Table 7
Differences in M Gene-End Signal Between
RSV 2B and 2B33F strains

	<u>Nucleotide Numbers</u>	<u>Nucleotide Sequence</u>
2B	4196-4207	A G G T A A A T A A A A
2B33F	4197-4208	A G G C A A A T A A A A
2B33F TS(+)	4197-4208	A G G C A A A T A A A A

↑

Table 8
RSV 2B, *ts* and Revertant Strains

Sample	Source	In Vitro Phenotype		In Vivo Growth*			
		<i>ts</i>	<i>ca</i>	Cotton Rat	AGM		
		39/32°C ROP plaque morph	20/32°C Yield	Nasal turbينات	Lungs	Nasal Wash	Bronchial Lavage
RSV 2B	Wild-type Parent Strain	0.7 (WT)	0.0001	5.5 ^a 3.9 ^b (4/4)	5.8 ^a 5.2 ^b (4/4)	5.8 ^a (4/4)	4.7 ^a (4/4)
RSV 2B33F	<i>ca</i> , <i>ts</i> mutant isolated from 2B cold-passaged x 33	0.00007 (sp,int/wt)	0.04	≤1.6 ^a <1.9 ^b (1/4)	<1.5 ^a <1.2 ^b (0/4)	3.0 ^a (4/4)	<0.9 ^a (0/4)
RSV 2B33F - 5a TS(+)	2B33F spinner passage, plaque picked at 39°C	0.5 (WT)	0.03	≤1.7 ^a (1/4)	3.5 ^a (4/4)	4.2 ^a (4/4)	4.0 ^a (4/4)
RSV 2B33F - 4a TS(+)	2B33F spinner passage, plaque picked at 39°C	0.7 (WT)	0.01	≤1.7 ^a (3/4)	3.8 ^a (4/4)	ND	ND
RSV 2B33F - 3b TS(+)	2B33F spinner passage, plaque picked at 39°C	0.5 (WT)	0.04	≤2.5 ^a (3/4)	2.9 ^a (4/4)	ND	ND
AGM PP2	2B33F-infected AGM #A2,d7 nasal wash plaque picked at 32°C	0.3 (sp,int)	0.00002	≤2.0 ^b (1/4)	1.6 ^b (4/4)	ND	ND
AGM PP4	2B33F-infected AGM #A2,d7 nasal wash plaque picked at 32°C	0.1 (sp,int)	0.008	<1.6 ^b (0/4)	1.2 ^b (4/4)	ND	ND

Table 8 (continued)
RSV 2B, ts and Revertant Strains

Sample	Source	In Vitro Phenotype ts		In Vivo Growth* Cotton Rat			
		39/32°C EOP plaque morph	20/32°C yield	Nasal turbinate	Lungs	Nasal Wash	Bronchial Lavage
AGM pp6	2B33F-infected AGM #A4, d12 nasal wash plaque picked at 32°C	0.000004 (WT)	≤0.000005	≤1.5 ^b (1/4)	<1.1 ^b (0/4)	ND	ND
AGM pp7	2B33F-infected AGM #A4, d12 nasal wash plaque picked at 32°C	0.000004 (sp/int/wt)	0.007	≤1.4 ^b (1/4)	<1.0 ^b (0/4)	ND	ND
Chimp pp1A	2B33F-infected Chimp #1552, d4 tracheal lavage plaque picked at 32°C	0.5 (WT)	ND	ND	ND	ND	ND
Chimp pp3A	2B33F-infected Chimp #1560, d6 tracheal lavage plaque picked at 32°C	0.7 (WT)	ND	2.4 ^c (4/4)	≤3.0 ^c (3/4)	ND	ND
Chimp pp5A	2B33F-infected Chimp #1563, d10 nasal swab plaque picked at 32°C	0.7 (WT)	ND	≤2.3 ^c (3/4)	3.0 ^c (4/4)	ND	ND

* In Vivo growth measured in log₁₀ mean virus titer (# infected/# total)

ND = not done WT = wild-type plaque size sp = small plaque size int = intermediate plaque size

^a Dose = 10^{6.7} PFU IN^b Dose = 10^{5.6} PFU IN^c Dose = 10^{6.3} PFU IN

^d Dose = 10^{5.9} PFU IN^e Dose = 10^{6.6} PFU IN+IT^f Dose = 10^{6.0} PFU IN+IT

- 61 -

Table 9
2B33F Revertants

	<i>ts</i> (+) <i>In vitro</i>			AGM				Chimp		
	5a	4a	3b	pp2	pp4	pp6	pp7	1A	3A	5A
base no.†										
<u>M</u>										
4176,4200	S	S	S	S	S	S	S	S	S	S
<u>SH</u>										
14 bases*	S	S	S	S	S	S	S	S	S	S
<u>L</u>										
9560	S	S	S	S	S	S	S	S	S	S
9854	2B	2B	2B	S	S	S	S	2B	2B	2B
12187	S	S	S	S	S	S	S	S	S	S
14588	S	S	S	S	S	S	S	S	S	S
15072	S	S	S	S	S	S	S	S	S	S
Phenotype										
<i>ts</i>	2B	2B	2B	r	r	S	S	2B	2B	2B
<i>ca</i>	S	S	S	2B	S	2B	S	ND	ND	ND
Attenuated	r	r	r	(r)	(r)	S	S	ND	r	r

† These 2B33F revertant base nos. are one larger than for 2B for M, SH and L genes

* bases 4330,4410,4421,4443,4455,4485,4498,4506,4526,4527,4543, 4562,4576,4599

S = same base as 2B33F

2B = reversion to 2B base or complete reversion in phenotype

r = moderate reversion in phenotype

(r) = slight reversion in phenotype

ND = not done

- 62 -

Table 10
RSV 2B, *ts* and Revertant Strains: Phenotype Summary

Virus Isolate	Source	In Vitro Phenotype		In Vivo Attenuation	
		<i>ts</i>	<i>ca</i>	Cotton Rat	AGM
RSV 2B	Wild-type Parent Strain	-	-	-	-
RSV 2B33F	<i>ca</i> , <i>ts</i> mutant isolated from 2B, cold-passaged x 33	++++	++	++++	+++
RSV 2B33F - 5a TS(+)	2B33F spinner passage plaque picked at 39°C	-	++	++	+
RSV 2B33F - 4a TS(+)	2B33F spinner passage plaque picked at 39°C	-	++	++	ND
RSV 2B33F - 3b TS(+)	2B33F spinner passage plaque picked at 39°C	-	++	++	ND
AGM pp2	2B33F-infected AGM A2, d7 nasal wash plaque picked at 32°C	+	-	+++	ND
AGM pp4	2B33F-infected AGM A2, d7 nasal wash plaque picked at 32°C	+	++	+++	ND
AGM pp6	2B33F-infected AGM A4, d12 nasal wash plaque picked at 32°C	++++	-	++++	ND
AGM pp7	2B33F-infected AGM A4, d12 nasal wash plaque picked at 32°C	++++	++	++++	ND
Chimp pp1A	2B33F-infected chimp #1552, d4 tracheal lavage, plaque picked at 32°C	-	ND	ND	ND
Chimp pp3A	2B33F-infected chimp #1560, d6 tracheal lavage, plaque picked at 32°C	-	ND	++	ND
Chimp pp5A	2B33F-infected chimp #1563, d10 tracheal lavage, plaque picked at 32°C	-	ND	++	ND

ND = not done

- = wild-type phenotype, i.e., not temperature sensitive, not cold adapted, not attenuated

+ to ++++ = increasing levels of temperature sensitivity, cold-adaptation or attenuation

- 63 -

Northern blot analysis of poly (A)+ RNA isolated from RSV-infected Vero cells was performed using a mixture of ³²P-labelled riboprobes specific for the M gene of RSV subgroup A and B viruses to determine the effect of the M gene-end signal sequences on M gene transcription. The negative sense hybridization probes were T7 RNA polymerase transcripts synthesized *in vitro* from PCR products containing the T7 promoter sequence. As shown in Figure 4, Northern blot analysis using M gene probes depicted abundant monocistronic M gene transcripts for RSV subgroup A viruses, whereas bicistronic M:SH transcripts were predominant for subgroup B viruses. Bicistronic M:SH transcripts are likely to be constrained in their ability to translate the SH gene and thus represent a potential means for controlling viral SH gene expression. The 2B33F mutant (lane 5) and 2B33F TS(+) revertant (lane 6) strains produced practically no monocistronic M transcripts; the bulk of their transcription products were bicistronic and higher molecular weight read-through transcripts. Thus, these two strains have essentially stopped producing the SH protein.

In contrast, the wild-type subgroup B strains 2B, B1 and 18537 produced a slight excess of bicistronic over monocistronic mRNAs (lanes 3, 4, 7). The subgroup A 3A virus showed comparable levels of monocistronic and bicistronic products (lane 1). At the other extreme from what was observed for the 2B mutant strains was the M gene transcription pattern of the A2 virus (lane 2). For this strain, monocistronic M transcripts were produced in abundance, while read-through transcription was minimal.

Northern blot results were confirmed by a ribonuclease protection assay which was performed on the same poly (A)+ RNA that was used for the Northern

- 64 -

blot, in order to assess the ratio of monocistronic M and SH mRNAs to bicistronic M:SH for each RSV subgroup B virus. Riboprobes were used which were negative sense virus-specific ³²P-labelled transcripts of 284 nucleotides in length (B viruses) that spanned the M:SH gene junction. The full-length probe should be protected from RNase digestion predominantly by bicistronic M:SH transcripts. Monocistronic M and SH transcripts are expected to protect approximately 165 and 110 nucleotide probe fragments, respectively, from RNase digestion.

In an assay for 2B, 2B33F, and 2B33F TS(+) viral RNA shown in Figure 5, viral RNA or control yeast RNA was hybridized with 5 X 10⁴ cpm of probe; thereafter, the hybridized RNA was then digested with RNase T1 (diluted 1:100), precipitated with ethanol, and the protected probe fragments were separated on a denaturing 6% polyacrylamide gel.

Results of this ribonuclease protection assay are depicted in Figure 5. In this assay, the signal intensity of the protected probe fragment corresponding to bicistronic M:SH relative to that of monocistronic M for each virus was in agreement with the results obtained by Northern blotting with the M gene probes, that is, greater monocistronic signal for 2B and practically no monocistronic signal for 2B33F and 2B33F TS(+) (Fig. 5).

To evaluate the influence of the M gene-end signal on expression of the downstream SH gene, Northern blot analysis of poly (A)+ RNA of the RSV viruses was performed using negative sense ³²P-labelled riboprobes specific for the SH gene of an RSV subgroup A and B strain to appraise the influence of the M GE signal on expression of the downstream SH gene (see Figure 6). The pattern of SH gene transcripts produced

- 65 -

by each virus, that is, the level of monocistronic SH to bicistronic M:SH, was comparable to that observed for the M gene transcription products. Those RSV viruses that were inefficient in terminating M gene transcription at the M gene-end signal were also compromised in the synthesis of monocistronic SH transcripts. The 2B33F mutant and its TS(+) revertant synthesized practically no monocistronic product, but accumulated abundant M:SH transcripts. The wild-type 3A, 2B, B1 and 18537 viruses accumulated comparable levels of both transcription products, while the A2 strain produced monocistronic SH mRNA as the most abundant product of SH gene transcription. The transcripts identified by Northern blot analysis were quantitated by phosphorimager analysis and a relative ratio of monocistronic SH to bicistronic M:SH was determined for each virus. As shown in Table 11, the ratios ranged from 0.23 to 11.1, with the lowest values observed for the RSV subgroup B strains containing the mutation at the fourth nucleotide (T → C) of the M gene-end signal:

Table 11
Ratio of Monocistronic SH to Bicistronic M:SH
Transcripts in RSV Subgroup A and B Strains

<u>Virus</u>	<u>SH/M:SH</u>
2B	1.4
2B33F	0.23
2B33F TS(+)	0.29
B1	1.0
18537	0.76
A2	11.1
3A	2.2

- 66 -

Several significant observations can be drawn from these data: As shown in Table 6, there are relatively few sequence changes identified in the mutant strain: RSV 2B33F differs from parental RSV 2B by two changes at the 3' genomic promoter region, two changes at the non-coding 5'-end of the M gene, including one in the M gene-end signal, and four coding changes plus one non-coding (poly(A) motif) change in the RNA dependent RNA polymerase coding L gene. In addition, 14 changes mapped to the SH gene alone.

An attenuating mutation can be identified in the M gene-end signal of the attenuated virus strain 2B33F: The shift from a slight excess of bicistronic over monocistronic mRNAs in the wild-type 2B strain to the predominance of bicistronic transcription products in the 2B33F vaccine strain and the 2B33F TS(+) revertant strain provides evidence that the mutation in the M gene-end signal contributes to the attenuation phenotype of these latter two viral strains.

- 67 -

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88. U.S. Patent Application No. 08/059,444.

- 73 -

What is claimed is:

1. An isolated, recombinantly-generated, attenuated measles virus having one or more attenuating mutations selected from the group consisting of:

- (a) for the N gene, nucleotide changes which produce changes in an amino acid selected from the group consisting of residues 129 (glutamine → lysine), 148 (glutamic acid → glycine) and 479 (serine → threonine);
- (b) for the P gene, nucleotide changes which produce changes in an amino acid selected from the group consisting of residues 225 (glutamic acid → glycine), 275 (cysteine → tyrosine) and 439 (leucine → proline);
- (c) for the C gene, nucleotide changes which produce changes in an amino acid selected from the group consisting of residues 73 (alanine → valine), 104 (methionine → threonine) and 134 (serine → tyrosine); and
- (d) for the F gene-end signal, the change at nucleotide 7243 (T → C), where these nucleotides are presented in positive strand, antigenomic, message sense.

2. The measles virus of Claim 1 which further comprises:

- (a) at least one attenuating mutation in the 3' genomic promoter region selected from the group consisting of nucleotide 26 (A → T), nucleotide 42 (A → T or A → C) and nucleotide 96 (G → A), where these

- 74 -

- nucleotides are presented in positive strand, antigenomic, message sense; and
- (b) at least one attenuating mutation in the RNA polymerase gene selected from the group consisting of nucleotide changes which produce changes in an amino acid selected from the group consisting of residues 331 (isoleucine → threonine), 1409 (alanine → threonine), 1624 (threonine → alanine), 1649 (arginine → methionine), 1717 (aspartic acid → alanine), 1936 (histidine → tyrosine), 2074 (glutamine → arginine) and 2114 (arginine → lysine).

3. An isolated, recombinantly-generated, attenuated human respiratory syncytial virus (RSV) subgroup B having an attenuating mutation in the M gene-end signal at nucleotide 4199 (T → C), where these nucleotides are presented in positive strand, antigenomic, message sense.

4. The RSV subgroup B of Claim 3 which further comprises:

- (a) at least one attenuating mutation in the 3' genomic promoter region selected from the group consisting of nucleotide 4 (C → G) and the insertion of an additional A in the stretch of A's at nucleotides 6-11, where these nucleotides are presented in positive strand, antigenomic, message sense; and
- (b) at least one attenuating mutation in the RNA polymerase gene selected from the group consisting of nucleotide changes which produce changes in an amino acid

- 75 -

selected from the group consisting of residues 353 (arginine → lysine), 451 (lysine → arginine), 1229 (aspartic acid → asparagine), 2029 (threonine → isoleucine) and 2050 (asparagine → aspartic acid).

5. The RSV subgroup B of Claim 4 which includes the insertion of an additional A in the stretch of A's at nucleotides 6-11, such that the attenuating mutation in the M gene-end signal (T → C) is at nucleotide 4200, where these nucleotides are presented in positive strand, antigenomic, message sense.

6. A vaccine comprising an isolated, recombinantly-generated, attenuated measles virus according to Claim 1 and a physiologically acceptable carrier.

7. The vaccine of Claim 6 comprising a measles virus according to Claim 2 and a physiologically acceptable carrier.

8. A vaccine comprising an isolated, recombinantly-generated, attenuated RSV subgroup B according to Claim 3 and a physiologically acceptable carrier.

9. The vaccine of Claim 8 comprising an RSV subgroup B according to Claim 4 and a physiologically acceptable carrier.

10. The vaccine of Claim 8 comprising an RSV subgroup B according to Claim 5 and a physiologically acceptable carrier.

11. A method for immunizing an individual to induce protection against measles virus which comprises administering to the individual the vaccine of Claim 6.

- 76 -

12. The method of Claim 11 wherein the vaccine is the vaccine of Claim 7.

13. A method for immunizing an individual to induce protection against RSV subgroup B which comprises administering to the individual the vaccine of Claim 8.

14. The method of Claim 13 wherein the vaccine is the vaccine of Claim 9.

15. The method of Claim 13 wherein the vaccine is the vaccine of Claim 10.

16. A composition which comprises a transcription vector comprising an isolated nucleic acid molecule encoding a genome or antigenome of a measles virus according to Claim 1, together with at least one expression vector which comprises at least one isolated nucleic acid molecule encoding the trans-acting proteins N, P and L necessary for encapsidation, transcription and replication, whereby upon expression an infectious attenuated virus is produced.

17. The composition of Claim 16 wherein the transcription vector comprises an isolated nucleic acid molecule which encodes a measles virus according to Claim 2.

18. A composition which comprises a transcription vector comprising an isolated nucleic acid molecule encoding a genome or antigenome of an RSV subgroup B according to Claim 3, together with at least one expression vector which comprises at least one isolated nucleic acid molecule encoding the trans-acting proteins N, P, L and M2 necessary for encapsidation, transcription and replication, whereby upon expression an infectious attenuated RSV subgroup B is produced.

- 77 -

19. The composition of Claim 18 wherein the transcription vector comprises an isolated nucleic acid molecule which encodes an RSV subgroup B according to Claim 4.

20. The composition of Claim 18 wherein the transcription vector comprises an isolated nucleic acid molecule which encodes an RSV subgroup B according to Claim 5.

21. A method for producing infectious attenuated measles virus which comprises transforming or transfecting host cells with the at least two vectors of Claim 16 and culturing the host cells under conditions which permit the co-expression of these vectors so as to produce the infectious attenuated measles virus.

22. The method of Claim 21 wherein the virus is the measles virus of Claim 2.

23. A method for producing infectious attenuated RSV subgroup B which comprises transforming or transfecting host cells with the at least two vectors of Claim 18 and culturing the host cells under conditions which permit the co-expression of these vectors so as to produce the infectious attenuated RSV subgroup B.

24. The method of Claim 23 wherein the virus is the RSV subgroup B of Claim 4.

25. The method of Claim 23 wherein the virus is the RSV subgroup B of Claim 5.

1/6

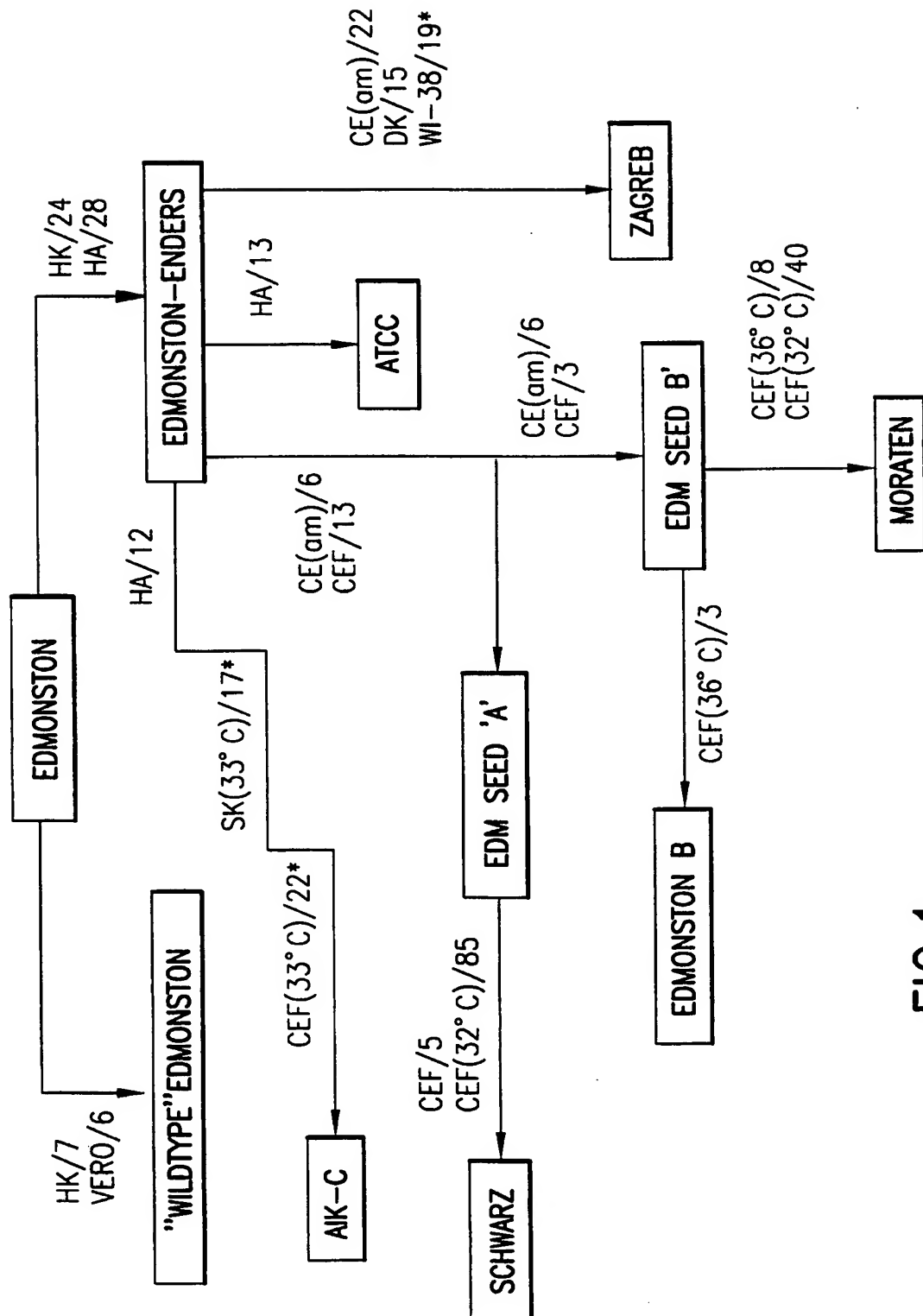
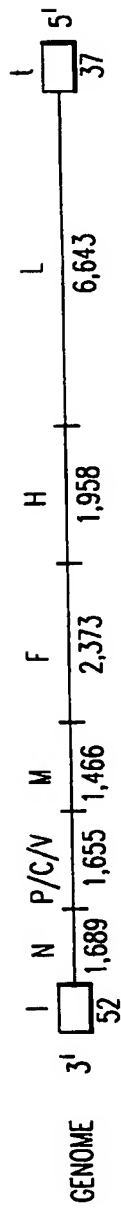


FIG.1

2/6



PUTATIVE EXTENDED PROMOTER AND REGULATORY REGIONS OF GENOME AND ANTIGENOME:
HIGHLY CONSERVED CIS-ACTING DOMAINS

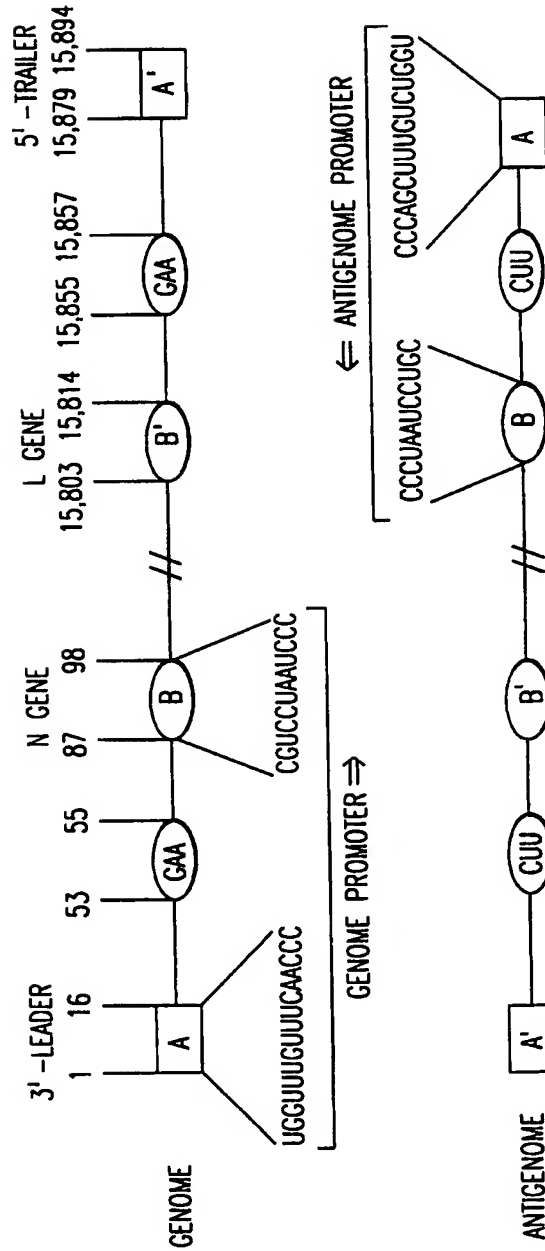


FIG.2

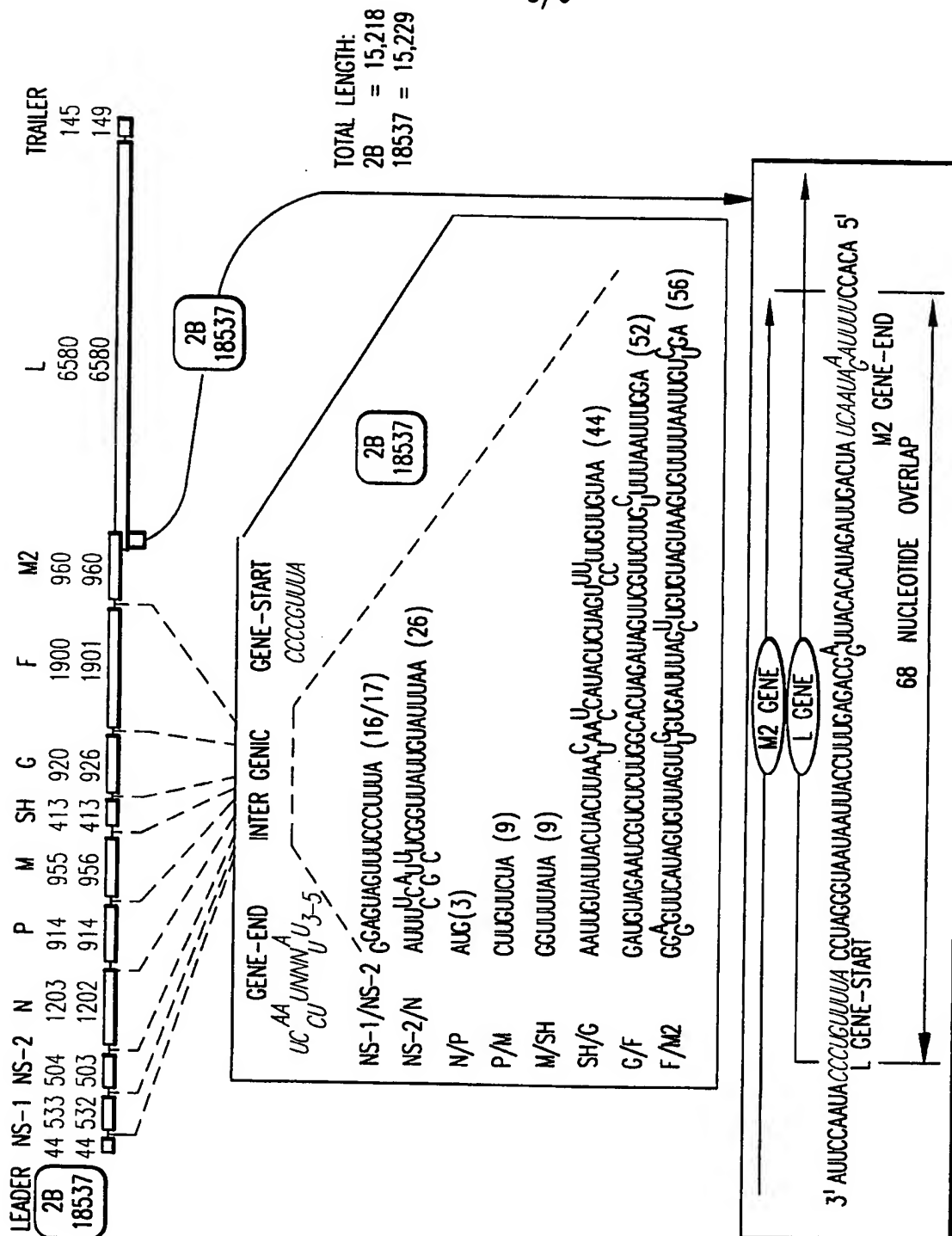


FIG. 3

SUBSTITUTE SHEET (RULE 26)

4/6

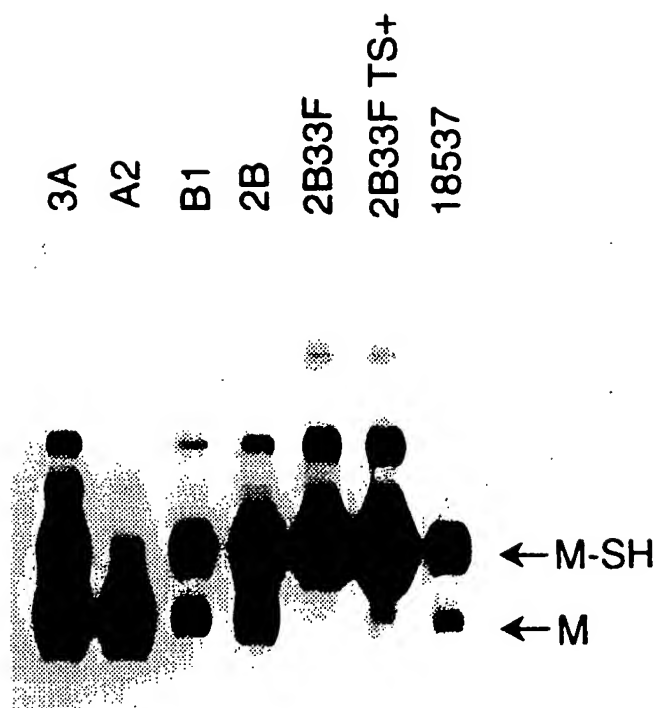


FIG.4

5/6

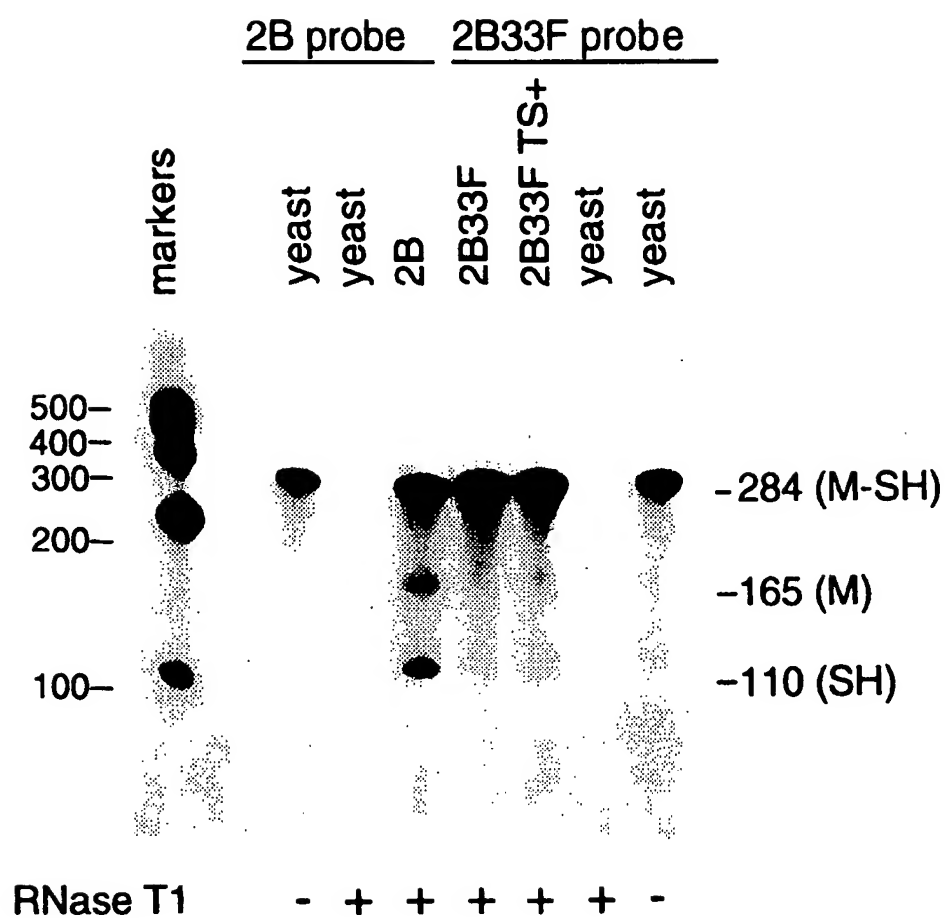


FIG. 5

6/6

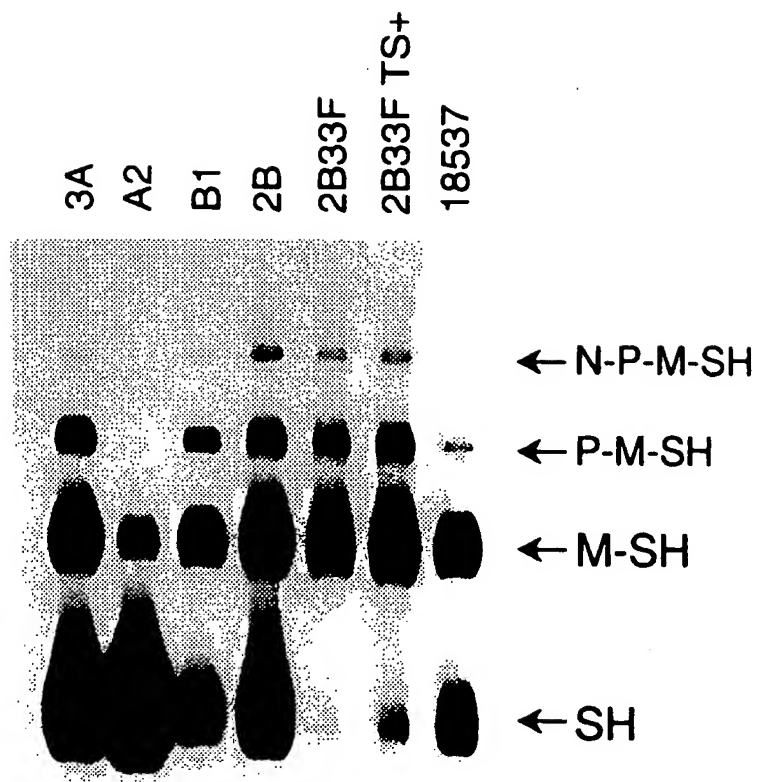


FIG.6

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